

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
15 May 2003 (15.05.2003)

PCT

(10) International Publication Number  
WO 03/040096 A2(51) International Patent Classification<sup>7</sup>: C07D

(21) International Application Number: PCT/US02/36072

(22) International Filing Date:  
8 November 2002 (08.11.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/337,122 8 November 2001 (08.11.2001) US  
60/344,086 28 December 2001 (28.12.2001) US  
60/345,635 3 January 2002 (03.01.2002) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

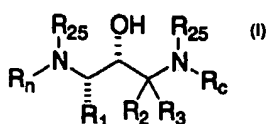
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

## Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: N, N'-SUBSTITUTED-1,3-DIAMINO-2-HYDROXYPROPANE DERIVATIVES

(57) Abstract: Disclosed are compounds of the formula (I), wherein the variables R<sub>N</sub>, R<sub>C</sub>, R<sub>1</sub>, R<sub>25</sub>, R<sub>2</sub>, and R<sub>3</sub> are as defined herein. These compounds have activity as inhibitors of betasecretase and are therefore useful in treating a variety of disorders such as Alzheimer's Disease.

## N,N'-SUBSTITUTED-1,3-DIAMINO-2-HYDROXYPROPANE DERIVATIVES

**BACKGROUND OF THE INVENTION****1. Field of the Invention**

5       The invention is directed to compounds useful in treatment of Alzheimer's disease and similar diseases.

**2. Description of the Related Art**

Alzheimer's disease (AD) is a progressive degenerative  
10 disease of the brain primarily associated with aging. Clinical  
ation of AD is characterized by loss of memory, cognition,  
reasoning, judgment, and orientation. As the disease  
progresses, motor, sensory, and linguistic abilities are also  
affected until there is global impairment of multiple cognitive  
15 functions. These cognitive losses occur gradually, but  
typically lead to severe impairment and eventual death in the  
range of four to twelve years.

Alzheimer's disease is characterized by two major  
pathologic observations in the brain: neurofibrillary tangles  
20 and beta amyloid (or neuritic) plaques, comprised predominantly  
of an aggregate of a peptide fragment know as A beta.  
Individuals with AD exhibit characteristic beta-amyloid  
deposits in the brain (beta amyloid plaques) and in cerebral  
blood vessels (beta amyloid angiopathy) as well as  
25 neurofibrillary tangles. Neurofibrillary tangles occur not  
only in Alzheimer's disease but also in other dementia-inducing  
disorders. On autopsy, large numbers of these lesions are  
generally found in areas of the human brain important for  
memory and cognition.

30       Smaller numbers of these lesions in a more restricted  
anatomical distribution are found in the brains of most aged  
humans who do not have clinical AD. Amyloidogenic plaques and  
vascular amyloid angiopathy also characterize the brains of  
individuals with Trisomy 21 (Down's Syndrome), Hereditary

Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D), and other neurogenerative disorders. Beta-amyloid is a defining feature of AD, now believed to be a causative precursor or factor in the development of the disease.

5 Deposition of A beta in areas of the brain responsible for cognitive activities is a major factor in the development of AD. Beta-amyloid plaques are predominantly composed of amyloid beta peptide (A beta, also sometimes designated betaA4). A beta peptide is derived by proteolysis of the amyloid precursor

10 protein (APP) and is comprised of 39-42 amino acids. Several proteases called secretases are involved in the processing of APP.

Cleavage of APP at the N-terminus of the A beta peptide by beta-secretase and at the C-terminus by one or more gamma-

15 secretases constitutes the beta-amyloidogenic pathway, i.e. the pathway by which A beta is formed. Cleavage of APP by alpha-secretase produces alpha-sAPP, a secreted form of APP that does not result in beta-amyloid plaque formation. This alternate pathway precludes the formation of A beta peptide.

20 An aspartyl protease has been identified as the enzyme responsible for processing of APP at the beta-secretase cleavage site. The beta-secretase enzyme has been disclosed using varied nomenclature, including BACE, Asp, and Memapsin.

Several lines of evidence indicate that progressive

25 cerebral deposition of beta-amyloid peptide (A beta) plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. Release of A beta from neuronal cells grown in culture and the presence of A beta in cerebrospinal fluid (CSF) of both normal individuals and AD

30 patients has been demonstrated.

It has been proposed that A beta peptide accumulates as a result of APP processing by beta-secretase, thus inhibition of this enzyme's activity is desirable for the treatment of AD. In vivo processing of APP at the beta-secretase cleavage site

is thought to be a rate-limiting step in A beta production, and is thus a therapeutic target for the treatment of AD.

BACE1 knockout mice fail to produce A beta, and a normal phenotype. When crossed with transgenic mice that overexpress  
5 APP, the progeny show reduced amounts of A beta in brain extracts as compared with control animals (Luo et. al., 2001 *Nature Neuroscience* 4:231-232). This evidence further supports the proposal that inhibition of beta-secretase activity and reduction of A beta in the brain provides a therapeutic method  
10 for the treatment of AD and other beta amyloid disorders.

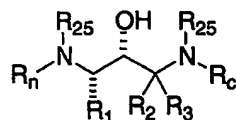
At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. Therefore, there is an urgent need for pharmaceutical agents capable of slowing the progression of Alzheimer's  
15 disease and/or preventing it in the first place.

Compounds that are effective inhibitors of beta-secretase, that inhibit beta-secretase-mediated cleavage of APP, that are effective inhibitors of A beta production, and/or are effective to reduce amyloid beta deposits or plaques, are needed for the  
20 treatment and prevention of disease characterized by amyloid beta deposits or plaques, such as AD.



SUMMARY OF INVENTION

In a broad aspect, the invention provides compounds of formula X:



- 5 and the pharmaceutically acceptable salts thereof wherein  
 $\text{R}_1$  is  $-(\text{CH}_2)_{1-2}-\text{S}(\text{O})_{0-2}-(\text{C}_1-\text{C}_6 \text{ alkyl})$ , or  
 $\text{C}_1-\text{C}_{10}$  alkyl optionally substituted with 1, 2, or 3 groups  
independently selected from halogen,  $-\text{OH}$ ,  $=\text{O}$ ,  $-\text{SH}$ ,  
 $-\text{C}\equiv\text{N}$ ,  $-\text{CF}_3$ ,  $-\text{C}_1-\text{C}_3$  alkoxy, amino, mono- or  
10 dialkylamino,  $-\text{N}(\text{R})\text{C}(\text{O})\text{R}'$ -,  $-\text{OC}(=\text{O})$ -amino and  
 $-\text{OC}(=\text{O})$ -mono- or dialkylamino, or  
 $\text{C}_2-\text{C}_6$  alkenyl or  $\text{C}_2-\text{C}_6$  alkynyl, each of which is optionally  
substituted with 1, 2, or 3 groups independently  
selected from halogen,  $-\text{OH}$ ,  $-\text{SH}$ ,  $-\text{C}\equiv\text{N}$ ,  $-\text{CF}_3$ ,  $\text{C}_1-\text{C}_3$   
15 alkoxy, amino, and mono- or dialkylamino, or  
aryl, heteroaryl, heterocyclyl,  $-\text{C}_1-\text{C}_6$  alkyl-aryl,  $-\text{C}_1-\text{C}_6$   
alkyl-heteroaryl, or  $-\text{C}_1-\text{C}_6$  alkyl-heterocyclyl, where  
the ring portions of each are optionally substituted  
with 1, 2, 3, or 4 groups independently selected from  
20 halogen,  $-\text{OH}$ ,  $-\text{SH}$ ,  $-\text{C}\equiv\text{N}$ ,  $-\text{NR}_{105}\text{R}'_{105}$ ,  $-\text{CO}_2\text{R}$ ,  $-\text{N}(\text{R})\text{COR}'$ ,  
or  $-\text{N}(\text{R})\text{SO}_2\text{R}'$ ,  $-\text{C}(=\text{O})-(\text{C}_1-\text{C}_4)$  alkyl,  $-\text{SO}_2$ -amino,  $-\text{SO}_2$ -  
mono or dialkylamino,  $-\text{C}(=\text{O})$ -amino,  $-\text{C}(=\text{O})$ -mono or  
dialkylamino,  $-\text{SO}_2-(\text{C}_1-\text{C}_4)$  alkyl, or  
 $\text{C}_1-\text{C}_6$  alkoxy optionally substituted with 1, 2, or 3  
25 groups which are independently selected from  
halogen, or  
 $\text{C}_3-\text{C}_7$  cycloalkyl optionally substituted with 1, 2, or  
3 groups independently selected from halogen,  $-\text{OH}$ ,  
 $-\text{SH}$ ,  $-\text{C}\equiv\text{N}$ ,  $-\text{CF}_3$ ,  $\text{C}_1-\text{C}_3$  alkoxy, amino,  $-\text{C}_1-\text{C}_6$   
30 alkyl and mono- or dialkylamino, or  
 $\text{C}_1-\text{C}_{10}$  alkyl optionally substituted with 1, 2, or 3  
groups independently selected from halogen,  $-\text{OH}$ ,

-SH, -C≡N, -CF<sub>3</sub>, -C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, mono- or dialkylamino and -C<sub>1</sub>-C<sub>3</sub> alkyl, or

C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>10</sub> alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, C<sub>1</sub>-C<sub>6</sub> alkyl and mono- or dialkylamino; and the heterocyclyl group is optionally further substituted with oxo;

where R and R' independently are hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkylaryl or C<sub>1</sub>-C<sub>10</sub> alkylheteroaryl;

R<sub>2</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, halogen hydroxy, -SH, cyano, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, or di(C<sub>1</sub>-C<sub>6</sub>)alkylamino;

R<sub>3</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, halogen hydroxy, -SH, cyano, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, or di(C<sub>1</sub>-C<sub>6</sub>)alkylamino:

or R<sub>2</sub> and R<sub>3</sub> are taken together with the carbon to which they are attached to form a 3 or 4-membered carbocyclic ring;

each R<sub>25</sub> is independently selected from the group consisting of hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>C</sub> is hydrogen, -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl, -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl, -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocyclyl, -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl-heteroaryl, -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl-heterocyclyl, -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-aryl-aryl, -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl-aryl, -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl-heterocyclyl, -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heteroaryl-heteroaryl, -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocyclyl-heteroaryl, -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocyclyl-heterocyclyl, -(CR<sub>245</sub>R<sub>250</sub>)<sub>0-4</sub>-heterocyclyl-aryl, -[C(R<sub>255</sub>)(R<sub>260</sub>)]<sub>1-3</sub>-CO-N-(R<sub>255</sub>)<sub>2</sub>, -CH(aryl)<sub>2</sub>,

-CH(heteroaryl)<sub>2</sub>, -CH(heterocyclyl)<sub>2</sub>,  
 -CH(aryl)(heteroaryl), -(CH<sub>2</sub>)<sub>0-1</sub>-CH((CH<sub>2</sub>)<sub>0-6</sub>-OH)-(CH<sub>2</sub>)<sub>0-1</sub>-  
 aryl, -(CH<sub>2</sub>)<sub>0-1</sub>-CH((CH<sub>2</sub>)<sub>0-6</sub>-OH)-(CH<sub>2</sub>)<sub>0-1</sub>-heteroaryl, -CH(-aryl  
 or -heteroaryl)-CO-O(C<sub>1</sub>-C<sub>4</sub> alkyl), -CH(-CH<sub>2</sub>-OH)-CH(OH)-  
 5 phenyl-NO<sub>2</sub>, (C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-OH; -CH<sub>2</sub>-NH-CH<sub>2</sub>-  
 CH(-O-CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-6</sub>-C(=NR<sub>235</sub>)(NR<sub>235</sub>R<sub>240</sub>), or  
 C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1, 2, or 3 groups  
 independently selected from the group consisting of  
 R<sub>205</sub>, -OC=ONR<sub>235</sub>R<sub>240</sub>, -S(=O)<sub>0-2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), -SH,  
 10 -NR<sub>235</sub>C=ONR<sub>235</sub>R<sub>240</sub>, -C=ONR<sub>235</sub>R<sub>240</sub>, and -S(=O)<sub>2</sub>NR<sub>235</sub>R<sub>240</sub>, or  
 -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>8</sub>) cycloalkyl wherein the cycloalkyl is  
 optionally substituted with 1, 2, or 3 groups  
 independently selected from the group consisting of  
 R<sub>205</sub>, -CO<sub>2</sub>H, and -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), or  
 15 cyclopentyl, cyclohexyl, or cycloheptyl ring fused to  
 aryl, heteroaryl, or heterocyclyl wherein one, two  
 or three carbons of the cyclopentyl, cyclohexyl, or  
 cycloheptyl is optionally replaced with a heteroatom  
 independently selected from NH, NR<sub>215</sub>, O, or S(=O)<sub>0-2</sub>,  
 20 and wherein the cyclopentyl, cyclohexyl, or  
 cycloheptyl group can be optionally substituted with  
 one or two groups that are independently R<sub>205</sub>, =O,  
 -CO-NR<sub>235</sub>R<sub>240</sub>, or -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), or  
 C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>10</sub> alkynyl, each of which is  
 25 optionally substituted with 1, 2, or 3 R<sub>205</sub> groups,  
 wherein  
 each aryl and heteroaryl is optionally substituted with 1,  
 2, or 3 R<sub>200</sub>, and wherein each heterocyclyl is  
 optionally substituted with 1, 2, 3, or 4 R<sub>210</sub>;  
 30 R<sub>200</sub> at each occurrence is independently selected from -OH,  
 -NO<sub>2</sub>, halogen, -CO<sub>2</sub>H, C≡N, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>220</sub>R<sub>225</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-  
 CO-(C<sub>1</sub>-C<sub>12</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub> alkenyl), -(CH<sub>2</sub>)<sub>0-4</sub>-  
 CO-(C<sub>2</sub>-C<sub>12</sub> alkynyl), -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-  
 CO-aryl, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-heteroaryl, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-

heterocyclyl,  $-(CH_2)_{0-4}-CO-O-R_{215}$ ,  $-(CH_2)_{0-4}-SO_2-NR_{220}R_{225}$ ,  $-(CH_2)_{0-4}-SO-(C_1-C_8 \text{ alkyl})$ ,  $-(CH_2)_{0-4}-SO_2-(C_1-C_{12} \text{ alkyl})$ ,  $-(CH_2)_{0-4}-SO_2-(C_3-C_7 \text{ cycloalkyl})$ ,  $-(CH_2)_{0-4}-N(H \text{ or } R_{215})-CO-O-R_{215}$ ,  $-(CH_2)_{0-4}-N(H \text{ or } R_{215})-CO-N(R_{215})_2$ ,  $-(CH_2)_{0-4}-N-CS-N(R_{215})_2$ ,  $-(CH_2)_{0-4}-N(-H \text{ or } R_{215})-CO-R_{220}$ ,  $-(CH_2)_{0-4}-NR_{220}R_{225}$ ,  $-(CH_2)_{0-4}-O-CO-(C_1-C_6 \text{ alkyl})$ ,  $-(CH_2)_{0-4}-O-P(O)-(OR_{240})_2$ ,  $-(CH_2)_{0-4}-O-CO-N(R_{215})_2$ ,  $-(CH_2)_{0-4}-O-CS-N(R_{215})_2$ ,  $-(CH_2)_{0-4}-O-(R_{215})$ ,  $-(CH_2)_{0-4}-O-(R_{215})-COOH$ ,  $-(CH_2)_{0-4}-S-(R_{215})$ ,  $-(CH_2)_{0-4}-O-(C_1-C_6 \text{ alkyl optionally substituted with 1, 2, 3, or 5 - F})$ ,  $C_3-C_7 \text{ cycloalkyl}$ ,  $-(CH_2)_{0-4}-N(H \text{ or } R_{215})-SO_2-R_{220}$ ,  $-(CH_2)_{0-4}-C_3-C_7 \text{ cycloalkyl}$ , or  $C_1-C_{10} \text{ alkyl optionally substituted with 1, 2, or 3 } R_{205} \text{ groups, or } C_2-C_{10} \text{ alkenyl or } C_2-C_{10} \text{ alkynyl, each of which is optionally substituted with 1 or 2 } R_{205} \text{ groups, wherein the aryl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 groups that are independently } R_{205}, R_{210}, \text{ or } C_1-C_6 \text{ alkyl substituted with 1, 2, or 3 groups that are independently } R_{205} \text{ or } R_{210}, \text{ and wherein the heterocyclyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently } R_{210};$

$R_{205}$  at each occurrence is independently selected from  $C_1-C_6 \text{ alkyl}$ , halogen,  $-OH$ ,  $-O\text{-phenyl}$ ,  $-SH$ ,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_6 \text{ alkoxy}$ ,  $NH_2$ ,  $NH(C_1-C_6 \text{ alkyl})$  or  $N-(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ ;

$R_{210}$  at each occurrence is independently selected from halogen,  $C_1-C_6 \text{ alkoxy}$ ,  $C_1-C_6 \text{ haloalkoxy}$ ,  $-NR_{220}R_{225}$ ,  $OH$ ,  $C\equiv N$ ,  $-CO-(C_1-C_4 \text{ alkyl})$ ,  $-SO_2-NR_{235}R_{240}$ ,  $-CO-NR_{235}R_{240}$ ,  $-SO_2-(C_1-C_4 \text{ alkyl})$ ,  $=O$ , or

C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl or C<sub>3</sub>-C<sub>7</sub> cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R<sub>205</sub> groups;

R<sub>215</sub> at each occurrence is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(aryl), C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and -(CH<sub>2</sub>)<sub>0-2</sub>-(heteroaryl), -(CH<sub>2</sub>)<sub>0-2</sub>-(heterocyclyl), wherein

the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R<sub>205</sub> or R<sub>210</sub>, and wherein

the heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 R<sub>210</sub>;

R<sub>220</sub> and R<sub>225</sub> at each occurrence are independently selected from -H, -C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>2</sub> alkyl)-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), -C<sub>2</sub>-C<sub>6</sub> alkenyl, -C<sub>2</sub>-C<sub>6</sub> alkynyl, -C<sub>1</sub>-C<sub>6</sub> alkyl chain with one double bond and one triple bond, -aryl, -heteroaryl, and -heterocyclyl, or -C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with -OH, -NH<sub>2</sub> or halogen, wherein

the aryl, heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 R<sub>270</sub> groups

R<sub>235</sub> and R<sub>240</sub> at each occurrence are independently H, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>245</sub> and R<sub>250</sub> at each occurrence are independently selected from -H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkylaryl, C<sub>1</sub>-C<sub>4</sub> alkylheteroaryl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, -(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, and phenyl; or

R<sub>245</sub> and R<sub>250</sub> are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6, or 7 carbon atoms, where one carbon atom is optionally replaced by a heteroatom selected from -O-, -S-, -SO<sub>2</sub>-, and -NR<sub>220</sub>-;

- $R_{255}$  and  $R_{260}$  at each occurrence are independently selected from  
 -H,  $-(CH_2)_{1-2}-S(O)_{0-2}-(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_4 \text{ alkyl})$ -aryl,  
 $-(C_1-C_4 \text{ alkyl})$ -heteroaryl,  $-(C_1-C_4 \text{ alkyl})$ -heterocyclyl, -  
 aryl, -heteroaryl, -heterocyclyl,  $-(CH_2)_{1-4}-R_{265}-(CH_2)_{0-4}$ -  
 5 aryl,  $-(CH_2)_{1-4}-R_{265}-(CH_2)_{0-4}$ -heteroaryl,  $-(CH_2)_{1-4}-R_{265}-(CH_2)_{0-4}$ -heterocyclyl, or  
 $C_1-C_6$  alkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl or  $-(CH_2)_{0-4}-C_3-C_7$   
 cycloalkyl, each of which is optionally substituted  
 with 1, 2, or 3  $R_{205}$  groups, wherein  
 10 each aryl or phenyl is optionally substituted with 1, 2,  
 or 3 groups that are independently  $R_{205}$ ,  $R_{210}$ , or  
 $C_1-C_6$  alkyl substituted with 1, 2, or 3 groups that  
 are independently  $R_{205}$  or  $R_{210}$ , and wherein  
 each heterocyclyl is optionally substituted with 1, 2, 3,  
 15 or 4  $R_{210}$ ;  
 $R_{265}$  at each occurrence is independently -O-, -S- or  $-N(C_1-C_6 \text{ alkyl})$ -;  
 $R_{270}$  at each occurrence is independently  $R_{205}$ , halogen  $C_1-C_6$   
 alkoxy,  $C_1-C_6$  haloalkoxy,  $NR_{235}R_{240}$ , -OH,  $-C\equiv N$ ,  $-CO-(C_1-C_4$   
 20 alkyl),  $-SO_2-NR_{235}R_{240}$ ,  $-CO-NR_{235}R_{240}$ ,  $-SO_2-(C_1-C_4 \text{ alkyl})$ , =O,  
 or  
 $C_1-C_6$  alkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl or  $-(CH_2)_{0-4}-C_3-C_7$   
 cycloalkyl, each of which is optionally substituted  
 with 1, 2, or 3  $R_{205}$  groups;  
 25  $R_N$  is  $R'_{100}$ ,  $-SO_2R'_{100}$ ,  $-(CRR')_{1-6}R'_{100}$ ,  $-C(=O)-(CRR')_{0-6}R_{100}$ ,  $-C(=O)-$   
 $(CRR')_{1-6}-O-R'_{100}$ ,  $-C(=O)-(CRR')_{1-6}-S-R'_{100}$ ,  $-C(=O)-(CRR')_{1-6}-$   
 $C(=O)-R_{100}$ ,  $-C(=O)-(CRR')_{1-6}-SO_2-R_{100}$  or  $-C(=O)-(CRR')_{1-6}-$   
 $NR_{100}-R'_{100}$ ;  
 $R_{100}$  and  $R'_{100}$  independently re aryl, heteroaryl, -aryl-W-aryl, -  
 30 aryl-W-heteroaryl, -aryl-W-heterocyclyl, -heteroaryl-W-  
 aryl, -heteroaryl-W-heteroaryl, -heteroaryl-W-  
 heterocyclyl, -heterocyclyl-W-aryl, -heterocyclyl-W-  
 heteroaryl, -heterocyclyl-W-heterocyclyl,  $-CH[(CH_2)_{0-2}-O-$   
 $R_{150}]- (CH_2)_{0-2}$ -aryl,  $-CH[(CH_2)_{0-2}-O-R_{150}]- (CH_2)_{0-2}$ -heterocyclyl

or  $-\text{CH}[(\text{CH}_2)_{0-2}-\text{O}-\text{R}_{150}]-(\text{CH}_2)_{0-2}-\text{heteroaryl}$ , where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

- OR,  $-\text{NO}_2$ , halogen,  $-\text{C}\equiv\text{N}$ ,  $-\text{OCF}_3$ ,  $-\text{CF}_3$ ,  $-(\text{CH}_2)_{0-4}-\text{O}-$
- 5  $\text{P}(=\text{O})(\text{OR})(\text{OR}')$ ,  $-(\text{CH}_2)_{0-4}-\text{CO}-\text{NR}_{105}\text{R}'_{105}$ ,  $-(\text{CH}_2)_{0-4}-\text{O}-$   
 $(\text{CH}_2)_{0-4}-\text{CONR}_{102}\text{R}_{102}'$ ,  $-(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_1-\text{C}_{12} \text{ alkyl})$ ,  $-(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_2-\text{C}_{12} \text{ alkenyl})$ ,  $-(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_2-\text{C}_{12} \text{ alkynyl})$ ,  
 $-(\text{CH}_2)_{0-4}-\text{CO}-(\text{CH}_2)_{0-4}(\text{C}_3-\text{C}_7 \text{ cycloalkyl})$ ,  $-(\text{CH}_2)_{0-4}-\text{R}_{110}$ ,  
 $-(\text{CH}_2)_{0-4}-\text{R}_{120}$ ,  $-(\text{CH}_2)_{0-4}-\text{R}_{130}$ ,  $-(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_{110}$ ,  $-(\text{CH}_2)_{0-4}-$   
10  $\text{CO}-\text{R}_{120}$ ,  $-(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_{130}$ ,  $-(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_{140}$ ,  $-(\text{CH}_2)_{0-4}-\text{CO}-$   
 $\text{O}-\text{R}_{150}$ ,  $-(\text{CH}_2)_{0-4}-\text{SO}_2-\text{NR}_{105}\text{R}'_{105}$ ,  $-(\text{CH}_2)_{0-4}-\text{SO}-(\text{C}_1-\text{C}_8$   
 $\text{alkyl})$ ,  $-(\text{CH}_2)_{0-4}-\text{SO}_2-(\text{C}_1-\text{C}_{12} \text{ alkyl})$ ,  $-(\text{CH}_2)_{0-4}-\text{SO}_2-$   
 $(\text{CH}_2)_{0-4}-(\text{C}_3-\text{C}_7 \text{ cycloalkyl})$ ,  $-(\text{CH}_2)_{0-4}-\text{N}(\text{R}_{150})-\text{CO}-\text{O}-\text{R}_{150}$ ,  
 $-(\text{CH}_2)_{0-4}-\text{N}(\text{R}_{150})-\text{CO}-\text{N}(\text{R}_{150})_2$ ,  $-(\text{CH}_2)_{0-4}-\text{N}(\text{R}_{150})-\text{CS}-$   
15  $\text{N}(\text{R}_{150})_2$ ,  $-(\text{CH}_2)_{0-4}-\text{N}(\text{R}_{150})-\text{CO}-\text{R}_{105}$ ,  $-(\text{CH}_2)_{0-4}-\text{NR}_{105}\text{R}'_{105}$ ,  
 $-(\text{CH}_2)_{0-4}-\text{R}_{140}$ ,  $-(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$ ,  $-(\text{CH}_2)_{0-4}-\text{O}-$   
 $\text{P}(\text{O})-(\text{O}-\text{R}_{110})_2$ ,  $-(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-\text{N}(\text{R}_{150})_2$ ,  $-(\text{CH}_2)_{0-4}-\text{O}-\text{CS}-$   
 $\text{N}(\text{R}_{150})_2$ ,  $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{150})$ ,  $-(\text{CH}_2)_{0-4}-\text{O}-\text{R}_{150}'-\text{COOH}$ ,  $-$   
 $(\text{CH}_2)_{0-4}-\text{S}-(\text{R}_{150})$ ,  $-(\text{CH}_2)_{0-4}-\text{N}(\text{R}_{150})-\text{SO}_2-\text{R}_{105}$ ,  $-(\text{CH}_2)_{0-4}-$   
20  $\text{C}_3-\text{C}_7 \text{ cycloalkyl}$ ,  $(\text{C}_2-\text{C}_{10})\text{alkenyl}$ , or  $(\text{C}_2-\text{C}_{10})\text{alkynyl}$ ,  
or

$\text{R}_{100}$  is  $\text{C}_1-\text{C}_{10}$  alkyl optionally substituted with 1, 2, or 3  $\text{R}_{115}$  groups, or

- 25  $\text{R}_{100}$  is  $-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{O}-\text{C}_1-\text{C}_6 \text{ alkyl}$  or  $-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{S}-(\text{C}_1-\text{C}_6$   
 $\text{alkyl})$ , each of which is optionally substituted with 1, 2,  
or 3  $\text{R}_{115}$  groups, or

$\text{R}_{100}$  is  $\text{C}_3-\text{C}_8$  cycloalkyl optionally substituted with 1, 2, or 3  $\text{R}_{115}$  groups;

$\text{W}$  is  $-(\text{CH}_2)_{0-4}-$ ,  $-\text{O}-$ ,  $-\text{S}(\text{O})_{0-2}-$ ,  $-\text{N}(\text{R}_{135})-$ ,  $-\text{CR}(\text{OH})-$  or  $-\text{C}(\text{O})-$ ;

- 30  $\text{R}_{102}$  and  $\text{R}_{102}'$  independently are hydrogen, or

$\text{C}_1-\text{C}_{10}$  alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, aryl or  $-\text{R}_{110}$ ;

$\text{R}_{105}$  and  $\text{R}'_{105}$  independently are  $-\text{H}$ ,  $-\text{R}_{110}$ ,  $-\text{R}_{120}$ ,  $\text{C}_3-\text{C}_7$  cycloalkyl,  $-(\text{C}_1-\text{C}_2 \text{ alkyl})-(\text{C}_3-\text{C}_7 \text{ cycloalkyl})$ ,  $-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{O}-(\text{C}_1-\text{C}_3$

alkyl), C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, or C<sub>1</sub>-C<sub>6</sub> alkyl chain with one double bond and one triple bond, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with -OH or -NH<sub>2</sub>; or, C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, or

R<sub>105</sub> and R'<sub>105</sub> together with the atom to which they are attached form a 3 to 7 membered carbocyclic ring, where one member is optionally a heteratom selected from -O-, -S(O)<sub>0-2</sub>-, -N(R<sub>135</sub>)-, the ring being optionally substituted with 1, 2 or three R<sub>140</sub> groups;

R<sub>115</sub> at each occurrence is independently halogen, -OH, -CO<sub>2</sub>R<sub>102</sub>, -C<sub>1</sub>-C<sub>6</sub> thioalkoxy, -CO<sub>2</sub>-phenyl, -NR<sub>105</sub>R'<sub>135</sub>, -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub> alkyl), -C(=O)R<sub>180</sub>, R<sub>180</sub>, -CONR<sub>105</sub>R'<sub>105</sub>, -SO<sub>2</sub>NR<sub>105</sub>R'<sub>105</sub>, -NH-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl), -NH-C(=O)-OH, -NH-C(=O)-OR, -NH-C(=O)-O-phenyl, -O-C(=O)-(C<sub>1</sub>-C<sub>6</sub> alkyl), -O-C(=O)-amino, -O-C(=O)-mono- or dialkylamino, -O-C(=O)-phenyl, -O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-CO<sub>2</sub>H, -NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy or C<sub>1</sub>-C<sub>6</sub> haloalkoxy;

R<sub>135</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(aryl), -(CH<sub>2</sub>)<sub>0-2</sub>-(heteroaryl), or -(CH<sub>2</sub>)<sub>0-2</sub>-(heterocyclyl);

R<sub>140</sub> is heterocyclyl optionally substituted with 1, 2, 3, or 4 groups independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, and =O;

R<sub>150</sub> is hydrogen, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>2</sub> alkyl)-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl), C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> alkyl with one double bond and one triple bond, -R<sub>110</sub>, -R<sub>120</sub>, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, or 4 groups independently selected from -OH, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, R<sub>110</sub>, and halogen;



- $R_{150}'$  is  $C_3$ - $C_7$  cycloalkyl,  $-(C_1$ - $C_3$  alkyl)-( $C_3$ - $C_7$  cycloalkyl),  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_1$ - $C_6$  alkyl with one double bond and one triple bond,  $-R_{110}$ ,  $-R_{120}$ , or  $C_1$ - $C_6$  alkyl optionally substituted with 1, 2, 3, or 4 groups independently selected from  $-OH$ ,  $-NH_2$ ,  $C_1$ - $C_3$  alkoxy,  $R_{110}$ , and halogen;
- $R_{180}$  is selected from morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl, each of which is optionally substituted with 1, 2, 3, or 4 groups independently selected from  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halogen, hydroxy, cyano, nitro, amino, mono( $C_1$ - $C_6$ )alkylamino, di( $C_1$ - $C_6$ )alkylamino,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  haloalkoxy, amino( $C_1$ - $C_6$ )alkyl, mono( $C_1$ - $C_6$ )alkylamino( $C_1$ - $C_6$ )alkyl, di( $C_1$ - $C_6$ )alkylamino( $C_1$ - $C_6$ )alkyl, and  $=O$ ;
- $R_{110}$  is aryl optionally substituted with 1 or 2  $R_{125}$  groups;
- $R_{125}$  at each occurrence is independently halogen, amino, mono- or dialkylamino,  $-OH$ ,  $-C\equiv N$ ,  $-SO_2-NH_2$ ,  $-SO_2-NH-C_1-C_6$  alkyl,  $-SO_2-N(C_1-C_6$  alkyl) $_2$ ,  $-SO_2-(C_1-C_4$  alkyl),  $-CO-NH_2$ ,  $-CO-NH-C_1-C_6$  alkyl, or  $-CO-N(C_1-C_6$  alkyl) $_2$ , or  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl or  $C_2$ - $C_6$  alkynyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently selected from  $C_1$ - $C_3$  alkyl, halogen,  $-OH$ ,  $-SH$ ,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1$ - $C_3$  alkoxy, amino, and mono- and dialkylamino, or  $C_1$ - $C_6$  alkoxy optionally substituted with one, two or three of halogen;
- $R_{120}$  is heteroaryl, which is optionally substituted with 1 or 2  $R_{125}$  groups; and
- $R_{130}$  is heterocyclyl optionally substituted with 1 or 2  $R_{125}$  groups.

In another broad aspect, the invention provides compounds of Formula X where

R<sub>1</sub> is:

- (I) C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>7</sub> alkyl (optionally substituted with C<sub>1</sub>-C<sub>3</sub> alkyl and C<sub>1</sub>-C<sub>3</sub> alkoxy), -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, -NR<sub>1-a</sub>R<sub>1-b</sub>, and -OC=O-NR<sub>1-a</sub>R<sub>1-b</sub>, where R<sub>1-a</sub> and R<sub>1-b</sub> are independently at each occurrence -H or C<sub>1</sub>-C<sub>6</sub> alkyl,
- 10 (II) -CH<sub>2</sub>-S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl),  
(III) -CH<sub>2</sub>-CH<sub>2</sub>-S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl),  
(IV) C<sub>2</sub>-C<sub>6</sub> alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, -NR<sub>1-a</sub>R<sub>1-b</sub> where R<sub>1-a</sub> and R<sub>1-b</sub> are -H or C<sub>1</sub>-C<sub>6</sub> alkyl,
- 15 (V) C<sub>2</sub>-C<sub>6</sub> alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, -NR<sub>1-a</sub>R<sub>1-b</sub> where R<sub>1-a</sub> and R<sub>1-b</sub> are -H or C<sub>1</sub>-C<sub>6</sub> alkyl,
- 20 (VI) -(CH<sub>2</sub>)<sub>n1</sub>-(R<sub>1-aryl</sub>) where n<sub>1</sub> is zero or one and where R<sub>1-aryl</sub> is phenyl, naphthyl, indanyl, indenyl, dihydronaphthyl, or tetralinyl each of which is optionally substituted with one, two, three, four, or five of the following substituents on the
- 25 aryl ring:
- (A) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three substituents selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, -F, -Cl, -Br, -I, -OH, -SH, -NR<sub>1-a</sub>R<sub>1-b</sub>, -C≡N, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>3</sub> alkoxy,
- 30 (B) C<sub>2</sub>-C<sub>6</sub> alkenyl optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

(C) C<sub>2</sub>-C<sub>6</sub> optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

(D) -F, Cl, -Br and -I,

5 (E) -C<sub>1</sub>-C<sub>6</sub> haloalkoxy

(F) -C<sub>1</sub>-C<sub>6</sub> alkoxy

(G) -NR<sub>N-2</sub>R<sub>N-3</sub>,

(H) -OH,

(I) -C≡N,

10 (J) C<sub>3</sub>-C<sub>7</sub> cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

(K) -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl),

15 (L) -SO<sub>2</sub>-NR<sub>1-a</sub>R<sub>1-b</sub>,

(M) -CO-NR<sub>1-a</sub>R<sub>1-b</sub>,

(N) -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl),

(VII) -(CH<sub>2</sub>)<sub>n1</sub>-(R<sub>1</sub>-heteroaryl) where R<sub>1</sub>-heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indoliziny, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, 25 oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, 30 isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl,

dihydrobenzothiazinyl, benzopyranyl, benzothiopyranyl,  
 coumarinyl, isocoumarinyl, chromonyl, chromanonyl,  
 tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl,  
 dihydroisoquinolinonyl, dihydrocoumarinyl,  
 5 dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl,  
 benzoxazolinonyl, pyridinyl-N-oxide, pyrrolyl N-oxide,  
 pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide,  
 quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide,  
 isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-  
 10 oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-  
 oxide, oxazolyl N-oxide, thiazolyl N-oxide, indoliziny N-  
 oxide, indazolyl N-oxide, benzothiazolyl N-oxide,  
 benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide,  
 thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide,  
 15 benzothiopyranyl S-oxide, and benzothiopyranyl S,S-dioxide,

where the  $R_1$ -heteroaryl group is bonded to  $-(CH_2)_{n1}-$  by  
 any ring atom of the parent  $R_N$ -heteroaryl group substituted by  
 hydrogen such that the new bond to the  $R_1$ -heteroaryl group  
 replaces the hydrogen atom and its bond, where heteroaryl is  
 20 optionally substituted with one, two, three, four, or five of:

(1)  $C_1$ - $C_6$  alkyl optionally substituted with one, two  
 or three substituents selected from the group consisting of  $C_1$ -  
 $C_3$  alkyl, -F, -Cl, -Br, -I, -OH,  
 -SH,  $-NR_{1-a}R_{1-b}$ ,  $-C\equiv N$ ,  $-CF_3$ , and  $C_1$ - $C_3$  alkoxy,

25 (2)  $C_2$ - $C_6$  alkenyl with one or two double bonds,  
 optionally substituted with one, two or three substituents  
 selected from the group consisting of -F, -Cl, -OH, -SH,  $-C\equiv N$ ,  
 $-CF_3$ ,  $C_1$ - $C_3$  alkoxy, and  $-NR_{1-a}R_{1-b}$ ,

(3)  $C_2$ - $C_6$  alkynyl with one or two triple bonds,  
 30 optionally substituted with one, two or three substituents  
 selected from the group consisting of -F, -Cl, -OH, -SH,  $-C\equiv N$ ,  
 $-CF_3$ ,  $C_1$ - $C_3$  alkoxy, and  $-NR_{1-a}R_{1-b}$ ,

(4) -F, -Cl, -Br and -I,

(5)  $-C_1$ - $C_6$  haloalkoxy,

- (6)  $-C_1-C_6$  alkoxy
- (7)  $-NR_{N-2}R_{N-3}$ ,
- (8)  $-OH$ ,
- (9)  $-C\equiv N$ ,
- 5 (10)  $C_3-C_7$  cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of  $-F$ ,  $-Cl$ ,  $-OH$ ,  $-SH$ ,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_3$  alkoxy, and  $-NR_{1-a}R_{1-b}$ ,
- (11)  $-CO-(C_1-C_4 \text{ alkyl})$ ,
- 10 (12)  $-SO_2-NR_{1-a}R_{1-b}$ ,
- (13)  $-CO-NR_{1-a}R_{1-b}$ ,
- (14)  $-SO_2-(C_1-C_4 \text{ alkyl})$ , with the proviso that when  $n_1$  is zero  $R_{1-heteroaryl}$  is not bonded to the carbon chain by nitrogen,
- 15 (VIII)  $-(CH_2)_{n_1}-(R_{1-heterocycle})$  where  $n_1$  is as defined above and  $R_{1-heterocycle}$  is selected from the group consisting of morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl,
- 20 tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranal, tetrahydrothienyl S-oxide,
- 25 tetrahydrothienyl S,S-dioxide, homothiomorpholinyl S-oxide, dithianyl, pyranal, dihydrofuranyl, pyrrolidinonyl, imidazolidinonyl, imidazolidinondionyl, wherein each of the above is optionally fused to a benzene, pyridine, or pyrimidine ring, and
- 30 where the  $R_{1-heterocycle}$  group is bonded by any atom of the parent  $R_{1-heterocycle}$  group substituted by hydrogen such that the new bond to the  $R_{1-heterocycle}$  group replaces the hydrogen atom and its bond, where heterocycle is optionally substituted with one, two, three or four:

(1) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, -F, -Cl, -Br, -I, -OH, -SH, -NR<sub>1-a</sub>R<sub>1-b</sub>, -C≡N, -CF<sub>3</sub>, and C<sub>1</sub>-C<sub>3</sub> alkoxy,

5 (2) C<sub>2</sub>-C<sub>6</sub> alkenyl optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, -NR<sub>1-a</sub>R<sub>1-b</sub>,

(3) C<sub>2</sub>-C<sub>6</sub> alkynyl optionally substituted with one, two or three substituents independently selected from the group  
10 consisting of -F, -Cl, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

(4) -F, -Cl, -Br and -I,

(5) C<sub>1</sub>-C<sub>6</sub> alkoxy,

(6) -C<sub>1</sub>-C<sub>6</sub> haloalkoxy,

15 (7) -NR<sub>N-2</sub>R<sub>N-3</sub>,

(8) -OH,

(9) -C≡N,

(10) C<sub>3</sub>-C<sub>7</sub> cycloalkyl, optionally substituted with one, two or three substituents independently selected from the  
20 group consisting of -F, -Cl, -OH, -SH  
-C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

(11) -CO-(C<sub>1</sub>-C<sub>4</sub> alkyl),

(12) -SO<sub>2</sub>-NR<sub>1-a</sub>R<sub>1-b</sub>,

(13) -CO-NR<sub>1-a</sub>R<sub>1-b</sub>,

25 (14) -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl),

(15) =O, with the proviso that when n<sub>1</sub> is zero R<sub>1</sub>-heterocycle is not bonded to the carbon chain by nitrogen;  
where R<sub>2</sub> is selected from the group consisting of:

(I) -H,

30 (II) C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

(III)  $-(CH_2)_{0-4}-R_{30}$  where  $R_{30}$  is  $R_1$ -aryl,  $R_1$ -heteroaryl, or  $R_1$ -heterocycle

(IV)  $C_2-C_6$  alkenyl with one or two double bonds, optionally substituted with one, two or three substituents independently selected from the group consisting of

5  $-F$ ,  $-Cl$ ,  $-OH$ ,  $-SH$ ,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_3$  alkoxy, and  $-NR_{1-a}R_{1-b}$ ,

(V)  $C_2-C_6$  alkynyl optionally substituted with one, two or three substituents independently selected from the group consisting of  $-F$ ,  $-Cl$ ,  $-OH$ ,  $-SH$ ,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_3$  alkoxy, and

10  $-NR_{1-a}R_{1-b}$ ,

(VI)  $-(CH_2)_{0-4}-C_3-C_7$  cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of  $-F$ ,  $-Cl$ ,  $-OH$ ,  $-SH$ ,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_3$  alkoxy, and  $-NR_{1-a}R_{1-b}$ ,

15 where  $R_3$  is selected from the group consisting of:

(I)  $-H$ ,

(II)  $C_1-C_6$  alkyl, optionally substituted with one, two or three substituents selected from the group consisting of  $C_1-C_3$  alkyl,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-OH$ ,

20  $-SH$ ,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_3$  alkoxy, and  $-NR_{1-a}R_{1-b}$ ,

(III)  $-(CH_2)_{0-4}-R_{30}$ ,

(IV)  $C_2-C_6$  alkenyl,

(V)  $C_2-C_6$  alkynyl,

(VI)  $-(CH_2)_{0-4}-C_3-C_7$  cycloalkyl, optionally substituted

25 with one, two or three substituents independently selected from the group consisting of  $-F$ ,  $-Cl$ ,  $-OH$ ,  $-SH$ ,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_3$  alkoxy, and  $-NR_{1-a}R_{1-b}$ ,

or  $R_2$  and  $R_3$  are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six,

30 and seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of  $-O-$ ,  $-S-$ ,  $-SO_2-$ ,  $-NR_{N-2}-$ ;

$R_N$  is:

(I)  $R_{N-1}-X_N$  where  $X_N$  is selected from the group consisting of:

- (A)  $-\text{CO}-$ ,
- (B)  $-\text{SO}_2-$ ,
- 5 (C)  $-(\text{CR}'\text{R}'')_{1-6}$  wherein  
 $\text{R}'$  and  $\text{R}''$  at each occurrence are the same or different and are  $-\text{H}$  or  $\text{C}_1\text{-C}_4$  alkyl,
- (D)  $-\text{CO}-(\text{CR}'\text{R}'')_{1-6}-X_{N-1}$  wherein  $X_{N-1}$  is selected from the group consisting of  $-\text{O}-$ ,  $-\text{S}-$  and  $-\text{NR}'-$ ,
- 10 (E) a single bond, and
- (F)  $-\text{CO}-(\text{CR}'\text{R}'')_{1-6}-$

where  $R_{N-1}$  is selected from the group consisting of:

- (A)  $R_{N\text{-aryl}}$  wherein  $R_{N\text{-aryl}}$  at each occurrence is independently phenyl; naphthyl; tetralinyl; indanyl; indenyl;
- 15 dihydronaphthyl; or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl; each of which is optionally substituted with 1, 2, or 3 groups that at each occurrence are independently:

- (1)  $\text{C}_1\text{-C}_6$  alkyl, optionally substituted with
- 20 one, two or three substituents selected from the group consisting of  $\text{C}_1\text{-C}_3$  alkyl,  $-\text{F}$ ,  $-\text{Cl}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{OH}$ ,  $-\text{SH}$ ,  $-\text{C}\equiv\text{N}$ ,  $-\text{CF}_3$ ,  $\text{C}_1\text{-C}_3$  alkoxy, and  $-\text{NR}_{1-a}\text{R}_{1-b}$ , wherein  $\text{R}_{1-a}$  and  $\text{R}_{1-b}$  at each occurrence are independently  $\text{H}$  or  $\text{C}_1\text{-C}_6$  alkyl,

- (2)  $-\text{OH}$ ,
- 25 (3)  $-\text{NO}_2$ ,
- (4)  $-\text{F}$ ,  $-\text{Cl}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,
- (5)  $-\text{CO}_2\text{H}$ ,
- (6)  $-\text{C}\equiv\text{N}$ ,
- (7)  $-(\text{CH}_2)_{0-4}-\text{CO}-\text{NR}_{N-2}\text{R}_{N-3}$  wherein at each
- 30 occurrence  $\text{R}_{N-2}$  and  $\text{R}_{N-3}$  are the same or different and are selected from the group consisting of:

- (a)  $-\text{H}$ ,
- (b)  $\text{C}_1\text{-C}_8$  alkyl optionally substituted with one substituent selected from the group consisting of:



- (i) -OH,
- (ii) -NH<sub>2</sub>,
- (iii) phenyl,
- (c) -C<sub>1</sub>-C<sub>8</sub> alkyl optionally substituted
- 5 with 1, 2, or 3 groups that are independently -F, -Cl, -Br, or -I,
- (d) -C<sub>3</sub>-C<sub>8</sub> cycloalkyl,
- (e) -(C<sub>1</sub>-C<sub>2</sub> alkyl)-(C<sub>3</sub>-C<sub>8</sub> cycloalkyl),
- (f) -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl),
- 10 (g) -C<sub>2</sub>-C<sub>6</sub> alkenyl,
- (h) -C<sub>2</sub>-C<sub>6</sub> alkynyl,
- (i) -C<sub>1</sub>-C<sub>6</sub> alkyl chain with one double bond and one triple bond,
- (j) -R<sub>1</sub>-aryl,
- 15 (k) -R<sub>1</sub>-heteroaryl,
- (l) -R<sub>1</sub>-heterocycle, or
- (m) R<sub>N-2</sub>, R<sub>N-3</sub> and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or heteroaryl group, wherein said heterocycloalkyl or heteroaryl
- 20 group is optionally fused to a benzene, pyridine, or pyrimidine ring, and said groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that at each occurrence are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl),
- 25 alkyl), -OH, -C(O)NH<sub>2</sub>, -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> thioalkoxy, and C<sub>1</sub>-C<sub>6</sub> thioalkoxy C<sub>1</sub>-C<sub>6</sub> alkyl;

(B) -R<sub>N</sub>-heteroaryl where R<sub>N</sub>-heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indoliziny, indazolyl, benzisothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl,

oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl,  
 oxazolopyridinyl, imidazopyridinyl, isothiazolyl,  
 naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl,  
 isochromanlyl, chromanlyl, tetrahydroisoquinolinyl, isoindolinyl,  
 5 isobenzotetrahydrofuranlyl, isobenzotetrahydrothienyl,  
 isobenzothienyl, benzoxazolyl, pyridopyridinyl,  
 benzotetrahydrofuranlyl, benzotetrahydrothienyl, purinyl,  
 benzodioxolyl, triazinyl, henoxazinyl, phenothiazinyl,  
 pteridinyl, benzothiazolyl, imidazothiazolyl,  
 10 dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl,  
 dihydrobenzisothiazinyl, benzopyranlyl, benzothiopyranlyl,  
 coumarinyl, isocoumarinyl, chromonyl, chromanonyl,  
 tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl,  
 dihydroisoquinolinonyl, dihydrocoumarinyl,  
 15 dihydroisocoumarinyl, isoindolinonyl, benzodioxanlyl,  
 benzoxazolinonyl, pyridinyl-N-oxide, pyrrolyl N-oxide,  
 pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide,  
 quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide,  
 isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-  
 20 oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-  
 oxide, oxazolyl N-oxide, thiazolyl N-oxide, indoliziny N-  
 oxide, indazolyl N-oxide, benzothiazolyl N-oxide,  
 benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide,  
 thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide,  
 25 benzothiopyranlyl S-oxide, benzothiopyranlyl S,S-dioxide,  
 imidazopyrazolyl, quinazolinonyl, pyrazopyridyl,  
 benzooxadiazolyl, dihydropyrimidinonyl, and  
 dihydrobenzofuranonyl, where each of the above is optionally  
 fused to a benzene, pyridine, or pyrimidine ring,

30 where the  $R_{N\text{-heteroaryl}}$  group is bonded by any atom of  
 the parent  $R_{N\text{-heteroaryl}}$  group substituted by hydrogen such that  
 the new bond to the  $R_{N\text{-heteroaryl}}$  group replaces the hydrogen atom  
 and its bond, where heteroaryl is optionally substituted with  
 one, two, three, or four of:

- (1)  $C_1-C_6$  alkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF<sub>3</sub>,  $C_1-C_3$  alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
- 5 (2) -OH,  
 (3) -NO<sub>2</sub>,  
 (4) -F, -Cl, -Br, -I,  
 (5) -CO<sub>2</sub>H,  
 (6) -C≡N,
- 10 (7) -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>N-2</sub>R<sub>N-3</sub>,  
 (8) -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>1</sub>-C<sub>12</sub> alkyl),  
 (9) -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub> alkenyl),  
 (10) -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub> alkynyl),  
 (11) -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>3</sub>-C<sub>8</sub> cycloalkyl),  
 15 (12) -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>1-aryl</sub>,  
 (13) -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>1-heteroaryl</sub>,  
 (14) -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>1-heterocycle</sub>,  
 (15) -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>N-4</sub>,  
 (16) -(CH<sub>2</sub>)<sub>0-4</sub>-CO<sub>2</sub>-R<sub>N-5</sub>,  
 20 (17) -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-NR<sub>N-2</sub>R<sub>N-3</sub>,  
 (18) -(CH<sub>2</sub>)<sub>0-4</sub>-SO-(aryl C<sub>1</sub>-C<sub>8</sub> alkyl),  
 (19) -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>12</sub> alkyl),  
 (20) -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>8</sub> cycloalkyl),  
 (21) -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>N-5</sub>)-CO-O-R<sub>N-5</sub>,  
 25 (22) -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>N-5</sub>)-CO-N(R<sub>N-5</sub>)<sub>2</sub>,  
 (23) -(CH<sub>2</sub>)<sub>0-4</sub>-N-CS-N(R<sub>N-5</sub>)<sub>2</sub>,  
 (24) -(CH<sub>2</sub>)<sub>0-4</sub>-N(-H or R<sub>N-5</sub>)-CO-R<sub>N-2</sub>,  
 (25) -(CH<sub>2</sub>)<sub>0-4</sub>-NR<sub>N-2</sub>R<sub>N-3</sub>,  
 (26) -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>N-4</sub>,  
 30 (27) -(CH<sub>2</sub>)<sub>0-4</sub>-O-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl),  
 (28) -(CH<sub>2</sub>)<sub>0-4</sub>-O-P(O)-(OR<sub>100</sub>)<sub>2</sub>,  
 (29) -(CH<sub>2</sub>)<sub>0-4</sub>-O-CO-N(R<sub>N-5</sub>)<sub>2</sub>,  
 (30) -(CH<sub>2</sub>)<sub>0-4</sub>-O-CS-N(R<sub>N-5</sub>)<sub>2</sub>,  
 (31) -(CH<sub>2</sub>)<sub>0-4</sub>-O-(R<sub>N-5</sub>),

- (32)  $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5})-\text{COOH}$ ,
- (33)  $-(\text{CH}_2)_{0-4}-\text{S}-(\text{R}_{\text{N}-5})$ ,
- (34)  $-(\text{CH}_2)_{0-4}-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl optionally substituted with one, two, three, four, or five of } -\text{F})$ ,
- 5 (35)  $\text{C}_3-\text{C}_8 \text{ cycloalkyl}$ ,
- (36)  $\text{C}_2-\text{C}_6 \text{ alkenyl optionally substituted with } \text{C}_1-\text{C}_3 \text{ alkyl, } -\text{F, } -\text{Cl, } -\text{Br, } -\text{I, } -\text{OH, } -\text{SH, } -\text{C}\equiv\text{N, } -\text{CF}_3, \text{ C}_1-\text{C}_3 \text{ alkoxy, or } -\text{NR}_{1-\text{a}}\text{R}_{1-\text{b}}$ ,
- (37)  $\text{C}_2-\text{C}_6 \text{ alkynyl optionally substituted with } \text{C}_1-\text{C}_3 \text{ alkyl, } -\text{F, } -\text{Cl, } -\text{Br, } -\text{I, } -\text{OH, } -\text{SH, } -\text{C}\equiv\text{N, } -\text{CF}_3, \text{ C}_1-\text{C}_3 \text{ alkoxy, or } -\text{NR}_{1-\text{a}}\text{R}_{1-\text{b}}$ ,
- 10 (38)  $-(\text{CH}_2)_{0-4}-\text{N}(-\text{H or } \text{R}_{\text{N}-5})-\text{SO}_2-\text{R}_{\text{N}-2}$ ,
- (39)  $-(\text{CH}_2)_{1-4}-\text{C}_3-\text{C}_8 \text{ cycloalkyl}$ ,
- (C)  $\text{R}_{\text{N-aryl}}-\text{W}-\text{R}_{\text{N-aryl}}$ ,
- 15 (D)  $\text{R}_{\text{N-aryl}}-\text{W}-\text{R}_{\text{N-heteroaryl}}$ ,
- (E)  $\text{R}_{\text{N-aryl}}-\text{W}-\text{R}_{1-\text{heterocycle}}$ ,
- (F)  $\text{R}_{\text{N-heteroaryl}}-\text{W}-\text{R}_{\text{N-aryl}}$ ,
- (G)  $\text{R}_{\text{N-heteroaryl}}-\text{W}-\text{R}_{\text{N-heteroaryl}}$ ,
- (H)  $\text{R}_{\text{N-heteroaryl}}-\text{W}-\text{R}_{1-\text{heterocycle}}$ ,
- 20 (I)  $\text{R}_{\text{N-heterocycle}}-\text{W}-\text{R}_{\text{N-aryl}}$ ,
- (J)  $\text{R}_{\text{N-heterocycle}}-\text{W}-\text{R}_{\text{N-heteroaryl}}$ ,
- (K)  $\text{R}_{\text{N-heterocycle}}-\text{W}-\text{R}_{1-\text{heterocycle}}$ ,
- where W is
- (1)  $-(\text{CH}_2)_{1-4}-$ ,
- 25 (2)  $-\text{O}-$ ,
- (3)  $-\text{S}(\text{O})_{0-2}-$ ,
- (4)  $-\text{N}(\text{R}_{\text{N}-5})-$ ,
- (5)  $-\text{CO}-$ ; or
- (6) a bond;
- 30 (II)  $-\text{CO}-(\text{C}_1-\text{C}_{10} \text{ alkyl})$  wherein the alkyl is optionally substituted with one two or three substituents independently selected from the group consisting of:
- (A)  $-\text{OH}$ ,

- (B)  $-C_1-C_6$  alkoxy,  
 (C)  $-C_1-C_6$  thioalkoxy,  
 (D)  $-CO_2-R_{N-8}$  where  $R_{N-8}$  at each occurrence is independently -H,  $C_1-C_6$  alkyl or -phenyl which is optionally substituted with 1 or 2 groups that are independently halogen,  $C_1-C_4$  alkoxy,  $C_1-C_4$  alkyl or  $-C(O)NH_2$ ,  
 (E)  $-CO-NR_{N-2}R_{N-3}$ ,  
 (F)  $-CO-R_{N-4}$ ,  
 (G)  $-SO_2-(C_1-C_8 \text{ alkyl})$ ,  
 (H)  $-SO_2-NR_{N-2}R_{N-3}$ ,  
 (I)  $-NH-CO-(C_1-C_6 \text{ alkyl})$ ,  
 (J)  $-NH-CO-O-R_{N-8}$ ,  
 (K)  $-NR_{N-2}R_{N-3}$ ,  
 (L)  $-R_{N-4}$ ,  
 (M)  $-O-CO-(C_1-C_6 \text{ alkyl})$ ,  
 (N)  $-O-CO-NR_{N-8}R_{N-8}$ ,  
 (O)  $-O-(C_1-C_5 \text{ alkyl})-COOH$ ,  
 (P)  $-O-(C_1-C_6 \text{ alkyl})$  optionally substituted with one, two, or three groups that are independently -F, -Cl, -Br, or -I),  
 (Q)  $-NH-SO_2-(C_1-C_6 \text{ alkyl})$ ,  
 (R) halogen,  
 (S)  $-N(H \text{ or } R_{N-5})-SO_2-R_{N-2}$ ,  
 (T)  $-N(H \text{ or } R_{N-5})-CO-(R_{N-2})$ , and  
 (U)  $-SO_2-R_{N-2}$ ,  
 (V)  $R_{N-aryl}$ ;

(III)  $-CO-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$  wherein each alkyl is unsubstituted or independently substituted with one, two, or three substituents selected from the group consisting of :

- (A) -OH,  
 (B)  $-C_1-C_6$  alkoxy,  
 (C)  $-C_1-C_6$  thioalkoxy,  
 (D)  $-CO-O-R_{N-8}$ ,  
 (E)  $-CO-NR_{N-2}R_{N-3}$ ,

- (F)  $-\text{CO}-\text{R}_{\text{N}-4}$ ,  
 (G)  $-\text{SO}_2-(\text{C}_1-\text{C}_8 \text{ alkyl})$ ,  
 (H)  $-\text{SO}_2-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$ ,  
 (I)  $-\text{NH}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$ ,  
 5 (J)  $-\text{NH}-\text{CO}-\text{O}-\text{R}_{\text{N}-8}$ ,  
 (K)  $-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$ ,  
 (L)  $-\text{R}_{\text{N}-4}$ ,  
 (M)  $-\text{O}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$ ,  
 (N)  $-\text{O}-\text{CO}-\text{NR}_{\text{N}-8}\text{R}_{\text{N}-8}$ ,  
 10 (O)  $-\text{O}-(\text{C}_1-\text{C}_5 \text{ alkyl})-\text{CO}_2\text{H}$ ,  
 (P)  $-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl})$  optionally substituted with one, two, or three groups that are independently  $-\text{F}$ ,  $-\text{Cl}$ ,  $-\text{Br}$ , or  $-\text{I}$ ,  
 (Q)  $-\text{NH}-\text{SO}_2-(\text{C}_1-\text{C}_6 \text{ alkyl})$ ,  
 15 (R) halogen,  
 (S)  $-\text{N}(\text{H or } \text{R}_{\text{N}-5})-\text{SO}_2-\text{R}_{\text{N}-2}$ ,  
 (T)  $-\text{N}(\text{H or } \text{R}_{\text{N}-5})-\text{CO}-(\text{R}_{\text{N}-2})$ ,  
 (U)  $-\text{SO}_2-\text{R}_{\text{N}-2}$ , and  
 (V)  $\text{R}_{\text{N-aryl}}$ ;  
 20 (IV)  $-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{S}-(\text{C}_1-\text{C}_6 \text{ alkyl})$  wherein each alkyl is unsubstituted or substituted with one, two, or three of substituents independently selected from the group consisting of:  
 (A)  $-\text{OH}$ ,  
 25 (B)  $-\text{C}_1-\text{C}_6 \text{ alkoxy}$ ,  
 (C)  $-\text{C}_1-\text{C}_6 \text{ thioalkoxy}$ ,  
 (D)  $-\text{CO}-\text{O}-\text{R}_{\text{N}-8}$ ,  
 (E)  $-\text{CO}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$ ,  
 (F)  $-\text{CO}-\text{R}_{\text{N}-4}$ ,  
 30 (G)  $-\text{SO}_2-(\text{C}_1-\text{C}_8 \text{ alkyl})$ ,  
 (H)  $-\text{SO}_2-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$ ,  
 (I)  $-\text{NH}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$ ,  
 (J)  $-\text{NH}-\text{CO}-\text{O}-\text{R}_{\text{N}-8}$ ,  
 (K)  $-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$ ,

- (L)  $-R_{N-4}$ ,  
 (M)  $-O-CO-(C_1-C_6 \text{ alkyl})$ ,  
 (N)  $-O-CO-NR_{N-8}R_{N-8}$ ,  
 (O)  $-O-(C_1-C_5 \text{ alkyl})-COOH$ ,  
 5 (P)  $-O-(C_1-C_6 \text{ alkyl})$  optionally substituted with one, two, or three groups that are independently  $-F$ ,  $-Cl$ ,  $-Br$ , or  $-I$ ,  
 (Q)  $-NH-SO_2-(C_1-C_6 \text{ alkyl})$ ,  
 (R) halogen,  
 10 (S)  $-N(H \text{ or } R_{N-5})-SO_2-R_{N-2}$ ,  
 (T)  $-N(H \text{ or } R_{N-5})-CO-(R_{N-2})$ ,  
 (U)  $-SO_2-R_{N-2}$ , and  
 (V)  $R_{N-aryl}$ ;  
 (V)  $-CO-CH(-(CH_2)_{0-2}-O-R_{N-10})-(CH_2)_{0-2}-(R_{N-aryl} \text{ or } R_{N-heteroaryl})$

15 wherein

$R_{N-10}$  is selected from the group consisting of:

- (1)  $-H$ ,
- (2)  $C_1-C_6 \text{ alkyl}$ ,
- (3)  $C_3-C_8 \text{ cycloalkyl}$ ,
- 20 (4)  $C_2-C_6 \text{ alkenyl}$ ,
- (5)  $C_2-C_6 \text{ alkynyl}$ ,
- (6)  $R_1-aryl$ ,
- (7)  $R_{N-heteroaryl}$ ,
- (8)  $R_{N-heterocycle}$ ,
- 25 (VI)  $-CO-(C_3-C_8 \text{ cycloalkyl})$  where the cycloalkyl group is optionally substituted with one or two substituents independently selected from the group consisting of:
- (A)  $-(CH_2)_{0-4}-OH$ ,
- (B)  $-(CH_2)_{0-4}-C_1-C_6 \text{ alkoxy}$ ,
- 30 (C)  $-(CH_2)_{0-4}-C_1-C_6 \text{ thioalkoxy}$ ,
- (D)  $-(CH_2)_{0-4}-CO-O-R_{N-8}$ ,
- (E)  $-(CH_2)_{0-4}-CO-NR_{N-2}R_{N-3}$ ,
- (F)  $-(CH_2)_{0-4}-CO-R_{N-4}$ ,

- (G)  $-(CH_2)_{0-4}-SO_2-(C_1-C_8 \text{ alkyl}),$   
 (H)  $-(CH_2)_{0-4}-SO_2-NR_{N-2}R_{N-3},$   
 (I)  $-(CH_2)_{0-4}-NH-CO-(C_1-C_6 \text{ alkyl}),$   
 (J)  $-NH-CO-O-R_{N-8},$   
 5 (K)  $-(CH_2)_{0-4}-NR_{N-2}R_{N-3},$   
 (L)  $-(CH_2)_{0-4}-R_{N-4},$   
 (M)  $-O-CO-(C_1-C_6 \text{ alkyl}),$   
 (N)  $-O-CO-NR_{N-8}R_{N-8},$   
 (O)  $-O-(C_1-C_6 \text{ alkyl})-CO_2H,$   
 10 (P)  $-O-(C_1-C_6 \text{ alkyl})$  optionally substituted with one, two, or three groups that are independently selected from  $-F,$   $-Cl,$   $-Br,$  and  $-I),$   
 (Q)  $-NH-SO_2-(C_1-C_6 \text{ alkyl}),$   
 (R) halogen,  
 15 (S)  $-N(H \text{ or } R_{N-5})-SO_2-R_{N-2},$   
 (T)  $-N(H \text{ or } R_{N-5})-CO-(R_{N-2}),$   
 (U)  $-SO_2-R_{N-2},$  and  
 (V)  $R_{N-aryl};$

where  $R_C$  is:

- 20 (I)  $-C_1-C_{10}$  alkyl optionally substituted with one, two or three substituents selected from the group consisting of  $C_1-C_3$  alkyl,  $-F,$   $-Cl,$   $-Br,$   $-I,$   $-OH,$   $-SH,$   $-C\equiv N,$   $-CF_3,$   $C_1-C_6$  alkoxy,  $-O\text{-phenyl},$   $-NR_{1-a}R_{1-b},$   $-OC=O$   $NR_{1-a}R_{1-b},$   $-S(=O)_{0-2}$   $R_{1-a},$   $-NR_{1-a}C=O$   $NR_{1-a}R_{1-b},$   $-C=O$   $NR_{1-a}R_{1-b},$  and  $-S(=O)_2$   $NR_{1-a}R_{1-b},$   
 25 (II)  $-(CH_2)_{0-3}-(C_3-C_8)$  cycloalkyl where cycloalkyl can be optionally substituted with one, two or three substituents independently selected from the group consisting of  $C_1-C_3$  alkyl,  $-F,$   $-Cl,$   $-Br,$   $-I,$   $-OH,$   $-SH,$   $-C\equiv N,$   $-CF_3,$   $C_1-C_6$  alkoxy,  $-O\text{-phenyl},$   $-CO_2H,$   $-CO_2-(C_1-C_4 \text{ alkyl}),$  and  $-NR_{1-a}R_{1-b},$   
 30 (III)  $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}$  at each occurrence is independently phenyl; naphthyl; tetralinyl; indanyl; indenyl; dihydronaphthyl; or 6,7,8,9-tetrahydro-5H-



benzo[a]cycloheptenyl; each of which is optionally substituted with 1, 2, or 3 groups that at each occurrence are independently:

- (1) C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with one, two  
 5 or three substituents selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, -F, -Cl, -Br, -I,  
 -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

(2) -OH,

(3) -NO<sub>2</sub>,

10 (4) -F, -Cl, -Br, -I,

(5) -CO<sub>2</sub>H,

(6) -C≡N, and

(7) -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>N-2</sub>R<sub>N-3</sub>;

where R<sub>C-x</sub> and R<sub>C-y</sub> are independently

15 -H,

C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with one or two -  
 OH,

C<sub>1</sub>-C<sub>4</sub> alkoxy optionally substituted with 1, 2, or 3 -  
 F,

20 -(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>8</sub> cycloalkyl,

C<sub>2</sub>-C<sub>6</sub> alkenyl,

C<sub>2</sub>-C<sub>6</sub> alkynyl, and

phenyl,

or R<sub>C-x</sub> and R<sub>C-y</sub> are taken together with the carbon to which  
 25 they are attached to form a carbocycle of three, four, five,  
 six and seven carbon atoms, optionally where one carbon atom is  
 replaced by a heteroatom selected from the group consisting of  
 -O-, -S-, -SO<sub>2</sub>-, -NR<sub>N-2</sub>- and R<sub>C-aryl</sub> is defined as is defined  
 above;

30 (IV) -(CR<sub>C-x</sub>R<sub>C-y</sub>)<sub>0-4</sub>-R<sub>C-heteroaryl</sub> where R<sub>C-heteroaryl</sub> at each  
 occurrence is independently selected from the group consisting  
 of pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl,  
 indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl,  
 quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl,

isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzoisothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, isothiazolyl, 5 naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranlyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranlyl, benzotetrahydrothienyl, purinyl, 10 benzodioxolyl, triazinyl, henoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoquinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisoquinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, 15 tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, imidazopyrazolyl, quinazolinonyl, pyrazopyridyl, benzooxadiazolyl, dihydropyrimidinonyl, 20 dihydrobenzofuranonyl, pyridinyl-N-oxide, pyrrolyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N-oxide, 25 indazolyl N-oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide, and benzothiopyranyl S,S-dioxide,

30 where the R<sub>C</sub>-heteroaryl group is bonded by any atom of the parent R<sub>C</sub>-heteroaryl group substituted by hydrogen such that the new bond to the R<sub>C</sub>-heteroaryl group replaces the hydrogen atom and its bond, where heteroaryl is optionally substituted 1, 2, 3, or 4 groups that are independently:

(1)  $C_1-C_6$  alkyl, optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_3$  alkoxy, and  $-NR_{1-a}R_{1-b}$ ,

- 5 (2) -OH,
- (3)  $-NO_2$ ,
- (4) -F, -Cl, -Br, -I,
- (5) -CO-OH,
- (6)  $-C\equiv N$ ,
- 10 (7)  $-(CH_2)_{0-4}-CO-NR_{N-2}R_{N-3}$ ,
- (8)  $-(CH_2)_{0-4}-CO-(C_1-C_{12} \text{ alkyl})$ ,
- (9)  $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkenyl})$ ,
- (10)  $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkynyl})$ ,
- (11)  $-(CH_2)_{0-4}-CO-(C_3-C_7 \text{ cycloalkyl})$ ,
- 15 (12)  $-(CH_2)_{0-4}-CO-R_{1-aryl}$ ,
- (13)  $-(CH_2)_{0-4}-CO-R_{1-heteroaryl}$ ,
- (14)  $-(CH_2)_{0-4}-CO-R_{1-heterocycle}$ ,
- (15)  $-(CH_2)_{0-4}-CO-R_{N-4}$ ,
- (16)  $-(CH_2)_{0-4}-CO-O-R_{N-5}$ ,
- 20 (17)  $-(CH_2)_{0-4}-SO_2-NR_{N-2}R_{N-3}$ ,
- (18)  $-(CH_2)_{0-4}-SO-(C_1-C_8 \text{ alkyl})$ ,
- (19)  $-(CH_2)_{0-4}-SO_2-(C_1-C_{12} \text{ alkyl})$ ,
- (20)  $-(CH_2)_{0-4}-SO_2-(C_3-C_7 \text{ cycloalkyl})$ ,
- (21)  $-(CH_2)_{0-4}-N(H \text{ or } R_{N-5})-CO-O-R_{N-5}$ ,
- 25 (22)  $-(CH_2)_{0-4}-N(H \text{ or } R_{N-5})-CO-N(R_{N-5})_2$ ,
- (23)  $-(CH_2)_{0-4}-N-CS-N(R_{N-5})_2$ ,
- (24)  $-(CH_2)_{0-4}-N(-H \text{ or } R_{N-5})-CO-R_{N-2}$ ,
- (25)  $-(CH_2)_{0-4}-NR_{N-2}R_{N-3}$ ,
- (26)  $-(CH_2)_{0-4}-R_{N-4}$ ,
- 30 (27)  $-(CH_2)_{0-4}-O-CO-(C_1-C_6 \text{ alkyl})$ ,
- (28)  $-(CH_2)_{0-4}-O-P(O)-(OR_{100})_2$ ,
- (29)  $-(CH_2)_{0-4}-O-CO-N(R_{N-5})_2$ ,
- (30)  $-(CH_2)_{0-4}-O-CS-N(R_{N-5})_2$ ,
- (31)  $-(CH_2)_{0-4}-O-(R_{N-5})$ ,

- (32)  $-(CH_2)_{0-4}-O-(R_{N-5})-COOH$ ,  
 (33)  $-(CH_2)_{0-4}-S-(R_{N-5})$ ,  
 (34)  $-(CH_2)_{0-4}-O-(C_1-C_6 \text{ alkyl optionally substituted with one, two, three, four, or five of } -F)$ ,  
 5 (35)  $C_3-C_8 \text{ cycloalkyl}$ ,  
 (36)  $C_2-C_6 \text{ alkenyl optionally substituted with } C_1-C_3 \text{ alkyl, } -F, -Cl, -Br, -I, -OH, -SH, -C\equiv N, -CF_3, C_1-C_3 \text{ alkoxy, or } -NR_{1-a}R_{1-b}$ ,  
 (37)  $C_2-C_6 \text{ alkynyl optionally substituted with } C_1-C_3$   
 10  $\text{alkyl, } -F, -Cl, -Br, -I, -OH, -SH, -C\equiv N, -CF_3, C_1-C_3 \text{ alkoxy, or } -NR_{1-a}R_{1-b}$ ,  
 (38)  $-(CH_2)_{0-4}-N(-H \text{ or } R_{N-5})-SO_2-R_{N-2}$ , and  
 (39)  $-(CH_2)_{1-4}-(C_3-C_8 \text{ cycloalkyl})$ ,  
 (V)  $-(CR_{C-x}R_{C-y})_{0-4}-R_C\text{-aryl}-R_C\text{-aryl}$ ,  
 15 (VI)  $-(CR_{C-x}R_{C-y})_{0-4}-R_C\text{-aryl}-R_C\text{-heteroaryl}$ ,  
 (VII)  $-(CR_{C-x}R_{C-y})_{0-4}-R_C\text{-heteroaryl}-R_C\text{-aryl}$ ,  
 (VIII)  $-(CR_{C-x}R_{C-y})_{0-4}-R_C\text{-heteroaryl}-R_C\text{-heteroaryl}$ ,  
 (IX)  $-(CR_{C-x}R_{C-y})_{0-4}-R_C\text{-aryl}-R_C\text{-heterocycle}$ , wherein  
 $R_C\text{-heterocycle}$  is selected from the group consisting of  
 20 morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide,  
 thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl,  
 pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl,  
 tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl,  
 homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-  
 25 dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl,  
 dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl,  
 dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide,  
 tetrahydrothienyl S,S-dioxide, homothiomorpholinyl S-oxide,  
 dithianyl, pyranal, dihydrofuranyl, pyrrolidinonyl,  
 30 imidazolidinonyl, imidazolidinondionyl, wherein each of the  
 above is optionally fused to a benzene, pyridine, or pyrimidine  
 ring, and

where the  $R_{1\text{-heterocycle}}$  group is bonded by any atom of the  
 parent  $R_{1\text{-heterocycle}}$  group substituted by hydrogen such that the

new bond to the  $R_1$ -heterocycle group replaces the hydrogen atom and its bond, where heterocycle is optionally substituted with one, two, three or four:

(1)  $C_1$ - $C_6$  alkyl optionally substituted with one, two  
5 or three substituents independently selected from the group consisting of  $C_1$ - $C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH,  $-NR_{1-a}R_{1-b}$ ,  $-C\equiv N$ ,  $-CF_3$ , and  $C_1$ - $C_3$  alkoxy,

(2)  $C_2$ - $C_6$  alkenyl optionally substituted with one,  
two or three substituents selected from the group consisting of  
10 -F, -Cl, -OH, -SH,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1$ - $C_3$  alkoxy,  $-NR_{1-a}R_{1-b}$ ,

(3)  $C_2$ - $C_6$  alkynyl optionally substituted with one,  
two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1$ - $C_3$  alkoxy, and  $-NR_{1-a}R_{1-b}$ ,

15 (4) -F, -Cl, -Br and -I,

(5)  $C_1$ - $C_6$  alkoxy,

(6)  $-C_1$ - $C_6$  haloalkoxy,

(7)  $-NR_{N-2}R_{N-3}$ ,

(8) -OH,

20 (9)  $-C\equiv N$ ,

(10)  $C_3$ - $C_7$  cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH  
 $-C\equiv N$ ,  $-CF_3$ ,  $C_1$ - $C_3$  alkoxy, and  $-NR_{1-a}R_{1-b}$ ,

25 (11)  $-CO-(C_1-C_4 \text{ alkyl})$ ,

(12)  $-SO_2-NR_{1-a}R_{1-b}$ ,

(13)  $-CO-NR_{1-a}R_{1-b}$ ,

(14)  $-SO_2-(C_1-C_4 \text{ alkyl})$ ,

(15)  $=O$ , with the proviso that when  $n_1$  is zero  $R_1$ -  
30 heterocycle is not bonded to the carbon chain by nitrogen;

(X)  $-(CR_{C-x}R_{C-y})_{0-4}-R_C\text{-heteroaryl-}R_C\text{-heterocycle}$ ,

(XI)  $-(CR_{C-x}R_{C-y})_{0-4}-R_C\text{-heterocycle-}R_C\text{-aryl}$ ,

(XII)  $-(CR_{C-x}R_{C-y})_{0-4}-R_C\text{-heterocycle-}R_C\text{-heteroaryl}$ ,

(XIII) - (CR<sub>C-x</sub>R<sub>C-y</sub>)<sub>0-4</sub>-R<sub>C</sub>-heterocycle-R<sub>C</sub>-heterocycle,

(XIV) - (CR<sub>C-x</sub>R<sub>C-y</sub>)<sub>0-4</sub>-R<sub>C</sub>-heterocycle,

(XV) - [C(R<sub>C-1</sub>)(R<sub>C-2</sub>)]<sub>1-3</sub>-CO-N-(R<sub>C-3</sub>)<sub>2</sub> where R<sub>C-1</sub> and R<sub>C-2</sub> are the same or different and are selected from the group consisting of:

(A) -H,

(B) -C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, -F, -Cl, -Br, -I, -OH,

10 -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-phenyl, and -NR<sub>1-a</sub>R<sub>1</sub>,

(C) C<sub>2</sub>-C<sub>6</sub> alkenyl optionally substituted with one, two or three substituents selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-phenyl, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

15 (D) C<sub>2</sub>-C<sub>6</sub> alkynyl optionally substituted with one, two or three substituents selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-phenyl, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

(E) -(CH<sub>2</sub>)<sub>1-2</sub>-S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl),

20 (F) -(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>8</sub> cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-phenyl, and -NR<sub>1-a</sub>R<sub>1-b</sub>

(G) -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>C</sub>-aryl,

25 (H) -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>C</sub>-heteroaryl,

(I) -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>C</sub>-heterocycle,

(J) -R<sub>C</sub>-heteroaryl,

(K) -R<sub>C</sub>-heterocycle,

(M) -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>C-4</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>C</sub>-aryl where R<sub>C-4</sub> is -O-, -S-

30 or

-NR<sub>C-5</sub>- where R<sub>C-5</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl,

(N) -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>C-4</sub>-(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>C</sub>-heteroaryl,

(O) -R<sub>C</sub>-aryl,

and where  $R_{C-3}$  at each occurrence is the same or different and is:

- (A) -H,
- (B)  $-C_1-C_6$  alkyl optionally substituted with one, two  
5 or three substituents independently selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_6$  alkoxy, -O-phenyl, and  $-NR_{1-a}R_{1-b}$ ,
- (C)  $C_2-C_6$  alkenyl with one or two double bonds, optionally substituted with one, two or three substituents  
10 independently selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_6$  alkoxy, -O-phenyl, and  $-NR_{1-a}R_{1-b}$ ,
- (D)  $C_2-C_6$  alkynyl optionally substituted with one, two or three substituents independently selected from the group  
15 consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_6$  alkoxy, -O-phenyl, and  $-NR_{1-a}R_{1-b}$ ,
- (E)  $-(CH_2)_{0-4}-C_3-C_8$  cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -  
20 SH,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_6$  alkoxy, -O-phenyl,  $-NR_{1-a}R_{1-b}$ ,
- (F)  $-R_{C-aryl}$ ,
- (G)  $-R_{C-heteroaryl}$ ,
- (H)  $-R_{C-heterocycle}$ ,
- (I)  $-(C_1-C_4 \text{ alkyl})-R_{C-aryl}$ ,
- (J)  $-(C_1-C_4 \text{ alkyl})-R_{C-heteroaryl}$ ,
- (K)  $-(C_1-C_4 \text{ alkyl})-R_{C-heterocycle}$ ,
- (XVI)  $-CH(R_{C-aryl})_2$ ,
- (XVII)  $-CH(R_{C-heteroaryl})_2$ ,
- (XVIII)  $-CH(R_{C-aryl})(R_{C-heteroaryl})$ ,
- (XIX) -cyclopentyl, -cyclohexyl, or -cycloheptyl ring  
30 fused to  $R_{C-aryl}$  or  $R_{C-heteroaryl}$  or  $R_{C-heterocycle}$ , where one carbon of cyclopentyl, cyclohexyl, or -cycloheptyl is optionally replaced with NH,  $NR_{N-5}$ , O,  $S(=O)_{0-2}$ , and where cyclopentyl, cyclohexyl,

or -cycloheptyl can be optionally substituted with one or two -  
C<sub>1</sub>-C<sub>3</sub> alkyl, -F, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, =O, and -  
NR<sub>1-a</sub>R<sub>1-b</sub>,

(XX) C<sub>2</sub>-C<sub>10</sub> alkenyl optionally substituted with one, two or  
5 three substituents selected from the group consisting of C<sub>1</sub>-C<sub>3</sub>  
alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-  
phenyl, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

(XXI) C<sub>2</sub>-C<sub>10</sub> alkynyl optionally substituted with one, two  
or three substituents selected from the group consisting of C<sub>1</sub>-  
10 C<sub>3</sub> alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy,  
-O-phenyl, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

(XXI) -(CH<sub>2</sub>)<sub>0-1</sub>-CHR<sub>C-6</sub>-(CH<sub>2</sub>)<sub>0-1</sub>-R<sub>C</sub>-aryl where R<sub>C-6</sub> is -(CH<sub>2</sub>)<sub>0-6</sub>-  
OH,

(XXII) -(CH<sub>2</sub>)<sub>0-1</sub>-CHR<sub>C-6</sub>-(CH<sub>2</sub>)<sub>0-1</sub>-R<sub>C</sub>-heteroaryl,

15 (XXIII) -CH(-R<sub>C</sub>-aryl or R<sub>C</sub>-heteroaryl)-CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl),

(XXIV) -CH(-CH<sub>2</sub>-OH)-CH(-OH)-NO<sub>2</sub>,

(XXV) (C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-OH,

(XXVII) -CH<sub>2</sub>-NH-CH<sub>2</sub>-CH(-O-CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>,

(XXVIII) -H,

20 (XXIX) -(CH<sub>2</sub>)<sub>0-6</sub>-C(=NR<sub>1-a</sub>)(NR<sub>1-a</sub>R<sub>1-b</sub>);

R<sub>25</sub> at each occurrence is independently selected from the  
group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub>  
alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
alkanoyl, each of which is unsubstituted or substituted with 1,  
25 2, 3, or 4 groups independently selected from halogen, alkyl,  
hydroxy, alkoxy, and NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>, wherein

R<sub>26</sub> is selected from the group consisting of -C(O)-,  
-O-, -S-, -SO-, -SO<sub>2</sub>-, -CO<sub>2</sub>-, -C(O)NH-, and -C(O)N(C<sub>1</sub>-C<sub>6</sub>  
alkyl)-;

30 R<sub>27</sub> is selected from the group consisting of alkyl,  
alkoxy, phenyl, pyridyl, and cyclopropyl,  
and pharmaceutically acceptable salts thereof.



Disclosed is a method of treating a patient who has, or in preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for  
5 helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral  
10 Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated  
15 with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment which comprises administration of a therapeutically effective amount of a  
20 compound of the invention or a pharmaceutically acceptable salt thereof.

Also disclosed are methods for inhibiting beta-secretase activity, for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and  
25 Asp597, numbered for the APP-695 amino acid isotype; or at a corresponding site of an isotype or mutant thereof, for inhibiting production of amyloid beta peptide (A beta) in a cell, for inhibiting the production of beta-amyloid plaque in an animal, and for treating or preventing a disease  
30 characterized by beta-amyloid deposits in the brain which comprise administration of a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

The invention also discloses pharmaceutical compositions comprising compounds of the invention.

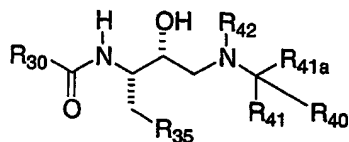
The invention provides compounds, compositions, kits, and methods for inhibiting beta-secretase-mediated cleavage of amyloid precursor protein (APP). More particularly, the compounds, compositions, and methods of the invention are effective to inhibit the production of A beta peptide and to treat or prevent any human or veterinary disease or condition associated with a pathological form of A beta peptide.

The compounds, compositions, and methods of the invention are useful for treating humans who have Alzheimer's Disease (AD), for helping prevent or delay the onset of AD, for treating patients with mild cognitive impairment (MCI), and preventing or delaying the onset of AD in those patients who would otherwise be expected to progress from MCI to AD, for treating Down's syndrome, for treating Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type, for treating cerebral beta-amyloid angiopathy and preventing its potential consequences such as single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, for treating dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type AD.

The compounds of the invention possess beta-secretase inhibitory activity. The inhibitory activities of the compounds of the invention are readily demonstrated, for example, using one or more of the assays described herein or known in the art.

## DETAILED DESCRIPTION OF THE INVENTION

In a specific aspect within Formula X, the invention provides compounds of formula Z1:



- 5 or a pharmaceutically acceptable salt thereof, wherein
- $R_{30}$  is selected from the group consisting of phenyl, pyrazolopyrimidinyl, oxa-aza-benzoazulenyl, isoxazolyl, triazolopyridinyl, pyrrolidinonyl, tetrahydrothia-aza-fluorenyl, pyridyl, piperidinyl, dihydrocyclopentaquinolinyl, furyl, naphthothienyl, phthalazinonyl, thiadiazolyl, thienopyrimidinonyl, oxa-diaza-cyclopentanaphthalenyl, dihydrobenzodioxepinyl, chromanonyl, chromenonyl, oxazolidinyl, benzophenone, pyrazinyl mono N-oxide, benzofuranyl, pyrazolyl, -isoxazolyl-phenyl, phenyl-triazolyl, benzimidazolyl, indolyl, phenyl-pyrrolyl, chromanyl, isoquinolinyl, -thienyl-thienyl, benzothienyl, -phenyl-thiadiazolyl, chromanonyl, quinolinyl, -pyrrolyl-C(O)-phenyl, -phenyl-O-phenyl, -phenyl-oxazolyl, -pyrrolidinonyl-phenyl, -phenyl-pyrimidinyl, -phenyl-oxadiazolyl, bicyclo[2.2.1]heptenyl, cyclopentyl, thieno[2,3-b]thiophene, cyclohexyl, -phenyl-imidazolyl, benzoxazole; dihydro-1H-indolyl; 2,3-dihydro-benzo[b]thiophene 1,1-dioxide; benzo[b]thiophene 1,1-dioxide; 2,3-dihydro-benzo[d]isothiazole 1,1-dioxide; -phenyl-thiazolyl; -phenyl-pyrazolyl, -phenyl-C(O)-piperidyl, -phenyl-C(O)-pyrrolidinyl, -phenyl-isoxazolyl, isoindolyl, purinyl, oxazolyl, thiazolyl, pyridazinonyl, thiazolyl, pyranyl, dihydropyranopyridinyl, diazepanyl, cyclopropyl, dihydronaphthoisoxazolyl, benzoindazole, dihydrocyclopentachromenonyl, imidazopyrazolyl, tetrahydrocyclopentachromenonyl, dihydroquinolinonyl, pyridyl N-oxide, isochromanyl, quinazolinonyl,
- 10
- 15
- 20
- 25
- 30

pyrazolopyridinyl, dihydrobenzothiophene dioxide,  
 dihydrofurobenzoisoxazolyl, dihydropyrimidine dionyl,  
 thienopyrazolyl, oxazolyl, tetrahydrocyclopentapyrazolyl,  
 dihydronaphthalenonyl, dihydrobenzofuranonyl,  
 5 dihydrocyclopentathienyl, tetrahydrocyclopentapyrazolyl,  
 tetrahydropyrazoloazepinyl, indazolyl,  
 tetrahydrocycloheptaisoxazolyl, tetrahydroindolonyl,  
 pyrrolidinyl, thienopyridinyl,  
 dioxodihydrobenzoisothiazolonyl, triazolopyrimidinyl,  
 10 thienyl, dihydrothienopyrimidinonyl, and benzooxadiazolyl,  
 wherein each of the above is unsubstituted or substituted  
 with 1, 2, 3, 4, or 5 groups that are independently  
 selected from the group consisting of  
 C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with 1 phenyl or 1 CN;  
 15 OH, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with  
 phenyl or (C<sub>1</sub>-C<sub>4</sub> alkyl)phenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy optionally  
 substituted with 1 or 2 groups that are independently  
 hydroxy or phenyl; haloalkyl, haloalkoxy, (CH<sub>2</sub>)<sub>0-4</sub>  
 C(O)NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl) wherein the alkyl  
 20 group is optionally substituted with 1, 2, or 3  
 groups that are independently halogen or R<sub>33</sub>, -SO<sub>2</sub>-  
 NH(C<sub>1</sub>-C<sub>6</sub> alkyl) wherein the alkyl group is optionally  
 substituted with 1 or 2 groups that are independently  
 halogen, OH, alkoxy, or R<sub>33</sub>; -(C<sub>1</sub>-C<sub>6</sub> alkyl)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>  
 25 alkyl) wherein the alkyl group is optionally  
 substituted with 1 or 2 groups that are independently  
 halogen, OH, C<sub>1</sub>-C<sub>4</sub> alkoxy, or R<sub>33</sub>; -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl)  
 wherein the alkyl group is optionally substituted  
 with 1 or 2 groups that are independently OH or C<sub>1</sub>-C<sub>4</sub>  
 30 alkoxy, -SO<sub>2</sub>-N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl) wherein each  
 alkyl group is optionally substituted with 1 or 2  
 groups that are independently halogen, OH or R<sub>33</sub>;  
 -SO<sub>2</sub>-NH(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl wherein the phenyl is  
 optionally substituted with 1 or 2 groups that are

independently C<sub>1</sub>-C<sub>4</sub> alkoxy or halogen, -O-(C<sub>1</sub>-C<sub>6</sub>  
alkyl)-phenyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-phenyl, -(C<sub>1</sub>-C<sub>6</sub>  
alkyl)-O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, triazolidine-3,5-  
dione, halogen, -NHC(O)NH<sub>2</sub>, -NHC(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl),  
5 -NHC(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub>  
alkyl)C(O)NH<sub>2</sub>, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl),  
-N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub>  
alkyl) thienyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl) furanyl, -S-(C<sub>1</sub>-C<sub>6</sub>  
alkyl) phenyl, -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(O)-NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>R<sub>32</sub>,  
10 dithiane, -NHC(S)NH<sub>2</sub>, -NHC(S)NH(C<sub>1</sub>-C<sub>6</sub> alkyl),  
-NHC(S)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -CO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl),  
tetrahydropyran, phenyl optionally substituted with 1  
or 2 groups that are independently F, Cl or Br;  
pyridine, -C<sub>2</sub>-C<sub>4</sub> alkynyl-phenyl, -O-C<sub>3</sub>-C<sub>8</sub> cycloalkyl,  
15 -O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-R<sub>33</sub>; pyrrole optionally substituted  
with one or two methyl groups; 2,3-dihydro-  
benzofuran; benzo[1,2,5]oxadiazole, -C(O)-(C<sub>1</sub>-C<sub>10</sub>  
alkyl) wherein the alkyl group is optionally  
substituted with NH<sub>2</sub>, N(C<sub>1</sub>-C<sub>6</sub> alkyl), or N(C<sub>1</sub>-C<sub>6</sub>  
alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); -C(O)NH-phenyl, -C(O)N(C<sub>1</sub>-C<sub>6</sub>  
20 alkyl)-phenyl, 4,4-dimethyl-4,5-dihydro-oxazole, -  
(C<sub>1</sub>-C<sub>6</sub> alkyl)-S-pyridine, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-SO<sub>2</sub>-pyridine,  
-(C<sub>1</sub>-C<sub>6</sub> thioalkoxy)-pyridine, thiazole optionally  
substituted with 1 or 2 methyl groups, pyrazole, S-  
25 (C<sub>1</sub>-C<sub>6</sub> alkyl), indole, (C<sub>1</sub>-C<sub>6</sub> thioalkoxy)-(C<sub>1</sub>-C<sub>6</sub>  
alkyl), C<sub>2</sub>-C<sub>8</sub> alkynyl, -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>10</sub>  
alkanoyl; -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>10</sub> alkyl) wherein the  
alkyl group is optionally substituted with OH;  
wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently  
30 selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>8</sub>  
alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>1</sub>-  
C<sub>6</sub> alkyl) wherein the alkyl is optionally substituted  
with 1, 2, 3 or 4 independently selected halogen

atoms;  $-(CH_2)_{0-4}-SO_2$ -imidazolyl,  $-(C_1-C_6 \text{ alkyl})-C(O)NH_2$ ,  $-(C_1-C_6 \text{ alkyl})-C(O)NH(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_6 \text{ alkyl})-C(O)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_6 \text{ alkyl})-NH_2$ ,  $-(C_1-C_6 \text{ alkyl})-NH(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_6 \text{ alkyl})-N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_6 \text{ alkyl})phenyl$ ,  $-(C_1-C_6 \text{ alkyl})pyridyl$ ,  $-C(O)furanyl$ ,  $(C_1-C_6 \text{ alkyl})-tetrahydrofuran$ ,  $cyclopropyl$ ,  $cyclobutyl$ ,  $cyclopentyl$ ,  $cyclohexyl$ ,  $-CO_2-(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_6 \text{ alkyl})-furanyl$ ,  $-(CH_2)_{0-4}-SO_2$ -thienyl, wherein

the phenyl and pyridyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently  $C_1-C_4$  alkyl, hydroxy,  $C_1-C_4$  alkoxy, halogen, or

$R_{31}$ ,  $R_{32}$  and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or a 6 membered heteroaryl ring, each of which is optionally fused to a benzene, pyridine or pyrimidine ring and each of which is optionally substituted with  $C_1-C_6$  alkoxy, hydroxy, hydroxy  $C_1-C_6$  alkyl,  $C_1-C_4$  alkoxy  $C_1-C_6$  alkyl,  $-C(O)NH_2$ ,  $-C(O)NH-(C_1-C_6 \text{ alkyl})-phenyl$ ;

$R_{33}$  at each occurrence is independently, H,  $NH_2$ ,  $NH(C_1-C_6 \text{ alkyl})$ ,  $N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ ,  $N(C_1-C_6 \text{ alkyl})(phenyl)$ ,  $N(C_1-C_6 \text{ alkyl})(benzyl)$ ;

$R_{35}$  is phenyl,  $C_3-C_8$  cycloalkyl,  $-S-phenyl$ , benzodioxole, thienyl,  $C_1-C_6$  alkyl, furanyl, imidazolyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy, OH, hydroxy  $C_1-C_6$  alkyl, halogen, halo  $C_1-C_6$  alkyl, halo  $C_1-C_6$  alkoxy,  $-O-(C_1-C_6 \text{ alkyl})-phenyl$ ,  $-CO_2-(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_4 \text{ alkyl})-(C_5-C_6 \text{ cycloalkyl})$ , or  $(CH_2)_{0-4}CN$ ;

$R_{40}$  is phenyl,  $-phenyl-pyridyl$ , biphenyl,  $-phenyl-benzothienyl$ ,  $-phenyl-thienyl$ ,  $-phenyl-furanyl$ ,  $-phenyl-pyrimidinyl$ ,  $-phenyl-isoxazolyl$ ,  $-C(O)-pyridyl$ ,  $-(C_1-C_4 \text{ alkyl})-O-C(O)NH-phenyl$  wherein the phenyl is optionally substituted with

1, 2, or 3 halogen atoms;  $-(C_1-C_4 \text{ alkyl})-O-C(O)N(C_1-C_6 \text{ alkyl})$ -phenyl,  $-(C_1-C_6 \text{ alkyl})$ -phenyl,  $-(C_1-C_4 \text{ alkyl})-SO_2NH_2$ ,  $-(C_1-C_4 \text{ alkyl})-SO_2NH(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_4 \text{ alkyl})-SO_2N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ ,  $-SO_2NH_2$ ,  $-SO_2NH(C_1-C_6 \text{ alkyl})$ ,  $-SO_2N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ , CN,  $-(CH_2)_{0-4}-(C_3-C_8 \text{ cycloalkyl})$ ,  $-(C_1-C_4 \text{ alkyl})-C(O)O-(C_1-C_4 \text{ alkyl})$ ,  $-(C_1-C_4 \text{ alkyl})-R_{33}$ ,  $C_1-C_{10} \text{ alkyl}$ ,  $C_2-C_8 \text{ alkenyl}$ ,  $-(C_1-C_4 \text{ alkyl})-NHC(O)-(C_1-C_4 \text{ alkyl})$ ,  $-(CH_2)_{0-4}-C(O)NH_2$ ,  $-(CH_2)_{0-4}-C(O)NH(C_1-C_6 \text{ alkyl})$ ,  $-(CH_2)_{0-4}-C(O)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ , naphthyl, tetrahydronaphthyl, dihydronaphthyl,  $-(CH_2)_{0-4}$ -imidazolyl,  $-(CH_2)_{0-4}$ -pyrrolidinyl, oxazolidinone 3,4-dihydro-benzo[e][1,2]oxathiine 2,2-dioxide, pyrimidinyl, 3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide, pyridyl, or pyrimidyl, alkoxyalkyl, -phenyl-benzothieryl, -phenyl-cyclohexyl, -phenyl-cyclopentyl, -phenyl- $(C_1-C_6 \text{ alkyl})$ -cyclopentyl, -phenyl- $(C_1-C_6 \text{ alkyl})$ -cyclohexyl, -phenyl-oxazolyl, furanyl, tetrahydrofuranyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen,  $C_1-C_8 \text{ alkyl}$  optionally substituted with 1 or two groups that are independently CN or OH;  $C_1-C_6 \text{ alkoxy}$ , halo  $(C_1-C_8 \text{ alkyl})$ , halo  $(C_1-C_4 \text{ alkoxy})$ ,  $-O-(C_1-C_4 \text{ alkyl})$ -phenyl wherein the phenyl is optionally substituted with 1 or 2 halogens, CN,  $-CHO$ ,  $C_1-C_4 \text{ thioalkoxy}$ ,  $-NHSO_2-(C_1-C_6 \text{ alkyl})$ ,  $-N(C_1-C_4 \text{ alkyl})SO_2-(C_1-C_4 \text{ alkyl})$  wherein the alkyl groups are optionally substituted with 1, 2, or 3 halogens; OH;  $-SO_2R_{33}$ ;  $R_{33}$ ;  $C_2-C_8 \text{ alkynyl}$ ;  $C_2-C_8 \text{ alkenyl}$ ; thioalkoxyalkyl;  $-SO_2-(C_1-C_{10} \text{ alkyl})$ ;  $-NR_{31}R_{32}$ ;  $-C(O)-NR_{31}R_{32}$ ;  $-OC(O)R_{33}$ ;  $C_1-C_8 \text{ alkanoyl}$ ;  $-(C_1-C_6 \text{ alkyl})-C(O)-(C_1-C_6 \text{ alkoxy})$ ;

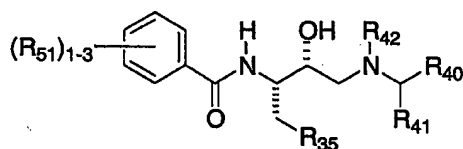
$R_{41a}$  and  $R_{41}$  are independently H, cyclohexyl, phenyl, or  $C_1-C_6 \text{ alkyl}$  optionally substituted with 1 or 2 groups that are phenyl, hydroxy,  $C_1-C_4 \text{ thioalkoxy}$ ,  $C_1-C_4 \text{ thioalkoxy } C_1-C_6 \text{ alkyl}$ ; or  $-C_1-C_6 \text{ alkyl}-SO_2-C_1-C_6 \text{ alkyl}$ ;

R<sub>40</sub>, R<sub>41</sub>, and the atom to which they are attached form a C<sub>3</sub>-C<sub>8</sub> cycloalkyl ring which is optionally substituted with C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, -CO<sub>2</sub>NH<sub>2</sub>, -CO<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -CO<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), thiazolyl optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, isoxazolyl optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, or phenyl which is optionally substituted with 1, 2, or 3 groups that are independently halogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

and

10 R<sub>42</sub> is H, C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with OH; benzyl; -NHC(O)-(C<sub>1</sub>-C<sub>6</sub> alkyl); -NHC(O)-phenyl wherein the phenyl is optionally substituted with 1 or 2 alkyl groups.

Preferred compounds of formula Z1 include the compounds of  
15 formula Z2:



Z2

or a pharmaceutically acceptable salt thereof, wherein

R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl) wherein the alkyl group is  
20 optionally substituted with 1, 2, or 3 halogens, -SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH<sub>2</sub>, -SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>1</sub>-C<sub>4</sub> alkyl), [1,2,4]triazolidine-3,5-dione, -NHC(O)NH<sub>2</sub>, -NHC(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl),  
25 -NHC(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)NH<sub>2</sub>, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), halogen, -CF<sub>3</sub>, OH, -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(O)NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>R<sub>32</sub>, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with phenyl or (C<sub>1</sub>-C<sub>4</sub> alkyl)phenyl,  
30 -O-(C<sub>1</sub>-C<sub>4</sub> alkyl)-phenyl, -NHC(S)NH<sub>2</sub>, -NHC(S)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -NHC(S)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), (C<sub>1</sub>-C<sub>4</sub> alkyl)-O-phenyl, -C(O)-(C<sub>1</sub>-C<sub>6</sub> alkyl) wherein the alkyl group is



optionally substituted with  $\text{NH}_2$ ,  $\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})$ , or  $\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{C}_1\text{-C}_6 \text{ alkyl})$ ;  $-\text{O}-\text{C}_3\text{-C}_6 \text{ cycloalkyl}$ , oxazole optionally substituted with 1, or 2 groups that are independently  $\text{C}_1\text{-C}_4 \text{ alkyl}$  or phenyl, hydroxy  $\text{C}_1\text{-C}_4 \text{ alkoxy}$ , aminoalkoxy,  $\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-alkoxy}$ ,  $\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-alkoxy}$ ,

wherein  $\text{R}_{31}$  and  $\text{R}_{32}$  at each occurrence are independently selected from the group consisting of hydrogen,  $\text{C}_1\text{-C}_6 \text{ alkyl}$ , hydroxy  $\text{C}_1\text{-C}_6 \text{ alkyl}$ ,  $\text{C}_1\text{-C}_6 \text{ haloalkyl}$ ,  $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-C}(\text{O})\text{NH}_2$ ,  $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-C}(\text{O})\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$ ,  $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-C}(\text{O})\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{C}_1\text{-C}_6 \text{ alkyl})$ ,  $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-NH}_2$ ,  $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$ ,  $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-N}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{C}_1\text{-C}_6 \text{ alkyl})$ ,  $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{phenyl}$ ,  $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{pyridyl}$ ,  $-\text{C}(\text{O})\text{furanyl}$ ,  $(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-tetrahydrofuran}$ , wherein the phenyl and pyridyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently  $\text{C}_1\text{-C}_4 \text{ alkyl}$ , hydroxy,  $\text{C}_1\text{-C}_4 \text{ alkoxy}$ , halogen, or

wherein at each occurrence  $\text{R}_{31}$ ,  $\text{R}_{32}$  and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, piperidinyl, azepanyl, pyridinyl, or pyrimidinyl ring, each of which is optionally fused to a benzene, pyridine or pyrimidine ring and each of which is optionally substituted with  $\text{C}_1\text{-C}_6 \text{ alkoxy}$ ,  $\text{C}_1\text{-C}_6 \text{ alkyl}$ , hydroxy, hydroxy  $\text{C}_1\text{-C}_6 \text{ alkyl}$ ,  $\text{C}_1\text{-C}_4 \text{ alkoxy C}_1\text{-C}_6 \text{ alkyl}$ ,  $-\text{C}(\text{O})\text{NH}_2$ , or  $-\text{C}(\text{O})\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-phenyl}$ .

Preferred compounds of Z2 are those wherein  $\text{R}_{41}$  and  $\text{R}_{42}$  are both hydrogen.

Other preferred compounds of Z2 are those wherein  $\text{R}_{35}$  is phenyl, cyclohexyl,  $-\text{S-phenyl}$ , benzodioxole, thienyl,  $\text{C}_3\text{-C}_6 \text{ alkyl}$ , furanyl, each of which is unsubstituted or substituted

with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>5</sub>-C<sub>6</sub> cycloalkyl).

5

Other preferred compounds of Z1 are those wherein

R<sub>35</sub> is phenyl, cyclohexyl, -S-phenyl, benzodioxole, thienyl, C<sub>3</sub>-C<sub>6</sub> alkyl, furanyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>5</sub>-C<sub>6</sub> cycloalkyl);

R<sub>40</sub> is phenyl, -phenyl-pyridine, biphenyl, -phenyl-benzothienyl, -phenyl-thienyl, -phenyl-furanyl, -phenyl-pyrimidinyl, -phenyl-isooxazolyl, -C(O)-pyridyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-C(O)NH-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), CN, -(CH<sub>2</sub>)<sub>0-4</sub>-(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-C(O)O-(C<sub>1</sub>-C<sub>4</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>33</sub>, C<sub>1</sub>-C<sub>8</sub> alkyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-NHC(O)-(C<sub>1</sub>-C<sub>4</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-C(O)NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), tetrahydronaphthyl, dihydronaphthyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halo (C<sub>1</sub>-C<sub>4</sub> alkyl), -O-(C<sub>1</sub>-C<sub>4</sub> alkyl)-phenyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, C<sub>1</sub>-C<sub>4</sub> thioalkoxy, -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl) wherein the alkyl groups are optionally substituted with 1, 2, or 3 halogens; OH, SO<sub>2</sub>R<sub>33</sub>, R<sub>33</sub>;

R<sub>41</sub> is H, cyclohexyl, phenyl, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or C<sub>1</sub>-C<sub>4</sub> thioalkoxy; and

R<sub>42</sub> is hydrogen or -CH<sub>2</sub>CN.

5

More preferred compounds of Z2 include those wherein

R<sub>35</sub> is phenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -S-phenyl, benzodioxole, thienyl, C<sub>3</sub>-C<sub>6</sub> alkyl, furanyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, CF<sub>3</sub>, OCF<sub>3</sub>, -Obenzyl, -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>5</sub>-C<sub>6</sub> cycloalkyl);

R<sub>40</sub> is phenyl, -phenyl-pyridine, biphenyl, -phenyl-benzothienyl, -phenyl-thienyl, -phenyl-furanyl, -phenyl-pyrimidinyl, -phenyl-isoxazolyl, -C(O)-pyridyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-C(O)NH-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), CN, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-C(O)O-(C<sub>1</sub>-C<sub>4</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>33</sub>, C<sub>1</sub>-C<sub>8</sub> alkyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-NHC(O)-(C<sub>1</sub>-C<sub>4</sub> alkyl), -C(O)NH<sub>2</sub>, wherein each of the above rings is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, -O-(C<sub>1</sub>-C<sub>4</sub> alkyl)-phenyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl) wherein the alkyl is optionally substituted with 1, 2, or 3 halogens,

R<sub>41</sub> is H, cyclohexyl, phenyl, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or C<sub>1</sub>-C<sub>4</sub> thioalkoxy; and

R<sub>42</sub> is hydrogen or -CH<sub>2</sub>CN;

R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl) wherein the alkyl group is

optionally substituted with 1, 2, or 3 halogens, -SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH<sub>2</sub>, -SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>1</sub>-C<sub>4</sub> alkyl), [1,2,4]triazolidine-3,5-dione, -NHC(O)NH<sub>2</sub>, -NHC(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -NHC(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)NH<sub>2</sub>, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), halogen, -CF<sub>3</sub>, OH, -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(O)NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>R<sub>32</sub>, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with phenyl or 2-methylphenyl, -O-(C<sub>1</sub>-C<sub>4</sub> alkyl)-phenyl, -NHC(S)NH<sub>2</sub>, -NHC(S)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -NHC(S)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), (C<sub>1</sub>-C<sub>4</sub> alkyl)-O-phenyl, -C(O)-(C<sub>1</sub>-C<sub>6</sub> alkyl) wherein the alkyl group is optionally substituted with NH<sub>2</sub>, N(C<sub>1</sub>-C<sub>6</sub> alkyl), or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); -O-C<sub>3</sub>-C<sub>6</sub> cycloalkyl, oxazole optionally substituted with 1, or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkoxy, aminoalkoxy, NH(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy, N(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy, wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)phenyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)pyridyl, -C(O)furanyl, (C<sub>1</sub>-C<sub>6</sub> alkyl)-tetrahydrofuran, wherein the phenyl group is unsubstituted or substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkoxy, or halogen, wherein at each occurrence R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, piperidinyl, or azepanyl, each of which is optionally fused to a benzene, pyridine or pyrimidine ring and each of which is optionally substituted with hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl,

hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NH<sub>2</sub>, or -C(O)NH-benzyl.

Even more preferred compounds of Z2 are those wherein

- 5 R<sub>35</sub> is phenyl; halophenyl, dihalophenyl; trihalophenyl; tetrahalophenyl; pentahalophenyl; halo, benzyloxyphenyl; halo, alkylphenyl; benzyloxyphenyl; cyclohexyl; (C<sub>1</sub>-C<sub>4</sub> alkoxy)carbonylphenyl; (C<sub>1</sub>-C<sub>4</sub> alkoxy)phenyl; -S-phenyl, or benzodioxole;
- 10 R<sub>41</sub> is H, cyclohexyl, phenyl, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or C<sub>1</sub>-C<sub>4</sub> thioalkoxy; and
- R<sub>42</sub> is hydrogen or -CH<sub>2</sub>CN.

15 Other preferred compounds of Z2 are those wherein

- R<sub>35</sub> is 3,5-dihalophenyl;
- R<sub>40</sub> is phenyl, -phenyl-pyridine, biphenyl, -phenyl-benzothienyl, -phenyl-thienyl, -phenyl-furanyl, -phenyl-pyrimidinyl, -phenyl-isoxazolyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-C(O)NH-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>NH<sub>2</sub>, CN, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-C(O)O-(C<sub>1</sub>-C<sub>4</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>33</sub>, or C<sub>1</sub>-C<sub>8</sub> alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently
- 20 halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, -O-(C<sub>1</sub>-C<sub>4</sub> alkyl)-phenyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, or -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl).
- 25

Even more preferred compounds of Z2 are those wherein

- 30 R<sub>35</sub> is 3,5-difluorophenyl; 3,5-dichlorophenyl; or 3-chloro,5-fluorophenyl; and
- R<sub>40</sub> is phenyl which is unsubstituted or substituted with 1, 2, or 3 groups that are independently fluoro, chloro, bromo, iodo, methyl, ethyl, methoxy, ethoxy, CF<sub>3</sub>, or -Obenzyl

wherein the phenyl is optionally substituted with 1 or 2 groups that are independently halogen, or -NHSO<sub>2</sub>CH<sub>3</sub>.

Even more preferred compounds of Z2 are those wherein  
5 R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NHSO<sub>2</sub>CH<sub>3</sub>, -SO<sub>2</sub>-NH-(ethyl)-NH(CH<sub>3</sub>), [1,2,4]triazolidine-3,5-dione, -NHC(O)NH<sub>2</sub>, -CF<sub>3</sub>, OH, -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(O)NR<sub>31</sub>R<sub>32</sub>, hydroxyoctyl, -CH(OH)-2-methylphenyl, -Obenzyl, or -NHC(S)NH(CH<sub>3</sub>);  
10 wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)C(O)N(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, benzyl, phenethyl, -CH<sub>2</sub>CH<sub>2</sub>pyridyl, -C(O)furanlyl, or  
15 at each occurrence R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, piperidinyl, or azepanyl, each of which is optionally substituted with hydroxymethyl, hydroxyethyl, methoxymethyl, or -C(O)NH<sub>2</sub>.

20

Even more preferred compounds of Z2 are those wherein  
R<sub>40</sub> is 3-ethylphenyl or 3-methoxyphenyl; and  
R<sub>42</sub> is hydrogen.

25 Preferred compounds of Z2 include those wherein  
R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -C(O)NR<sub>31</sub>R<sub>32</sub>, -C(O)CH<sub>2</sub>NH<sub>2</sub>, cyclopentyloxy, -NHC(O)NH(ethyl), oxazole optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl,  
30 hydroxyethoxy, diethylaminoethoxy,  
wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -CH<sub>2</sub>-tetrahydrofuran.

Other preferred compounds of Z2 include those wherein R<sub>35</sub> is cyclohexyl.

More preferred compounds include those wherein

- 5 R<sub>40</sub> is phenyl, or C<sub>1</sub>-C<sub>8</sub> alkyl, wherein each is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halo (C<sub>1</sub>-C<sub>4</sub> alkyl); and

R<sub>42</sub> and R<sub>41</sub> are both hydrogen.

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More preferred compounds include those wherein

- R<sub>40</sub> is phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-methylphenyl, 3-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, or C<sub>3</sub>-C<sub>6</sub> alkyl; and

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R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or halogen,

wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, and -(C<sub>1</sub>-C<sub>6</sub> alkyl)phenyl wherein the phenyl group is unsubstituted or substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkoxy, or halogen,

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wherein at each occurrence R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, piperidinyl, or azepanyl, each of which is optionally fused to a benzene, pyridine or pyrimidine ring and each of which is optionally substituted with hydroxy, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NH<sub>2</sub>, or -C(O)NH-benzyl.

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More preferred compounds include those wherein

R<sub>35</sub> is 3-halo, 5-benzyloxyphenyl; 3-benzyloxyphenyl; or 4-benzyloxyphenyl;

R<sub>41</sub> is H, cyclohexyl, phenyl, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or C<sub>1</sub>-C<sub>4</sub> thioalkoxy; and

R<sub>42</sub> is hydrogen or -CH<sub>2</sub>CN.

More preferred compounds include those wherein

R<sub>40</sub> is phenyl, -phenyl-pyridine, biphenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-C(O)NH-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-C(O)O-(C<sub>1</sub>-C<sub>4</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>33</sub>, or C<sub>1</sub>-C<sub>8</sub> alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, -Obenzyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, or -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl).

More preferred compounds include those wherein

R<sub>40</sub> is phenyl or C<sub>1</sub>-C<sub>8</sub> alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, -Obenzyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, or -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); and

R<sub>41</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or C<sub>1</sub>-C<sub>4</sub> thioalkoxy;

R<sub>42</sub> is hydrogen; and

R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl) wherein the alkyl group is optionally substituted with 1, 2, or 3 halogens, -SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH<sub>2</sub>, -SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>1</sub>-C<sub>4</sub> alkyl), -NHC(O)NH<sub>2</sub>, -NHC(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -NHC(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)NH<sub>2</sub>, -N(C<sub>1</sub>-C<sub>6</sub>



alkyl)C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), halogen, -CF<sub>3</sub>, OH, -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(O)NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>R<sub>32</sub>, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl, -Obenzyl, -NHC(S)NH<sub>2</sub>, -NHC(S)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -NHC(S)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), (C<sub>1</sub>-C<sub>4</sub> alkyl)-O-phenyl, -C(O)-(C<sub>1</sub>-C<sub>6</sub> alkyl), -O-cyclopentyl, -O-cyclohexyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkoxy, aminoalkoxy, NH(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy, N(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy,

wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), and benzyl wherein the phenyl group is unsubstituted or substituted with 1, or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkoxy, or halogen,

wherein at each occurrence R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, or piperidinyl, each of which is optionally substituted with hydroxy, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NH<sub>2</sub>, or -C(O)NH-benzyl.

More preferred compounds include those wherein

R<sub>40</sub> is phenyl or C<sub>1</sub>-C<sub>8</sub> alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or CF<sub>3</sub>; and

R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NHSO<sub>2</sub>CH<sub>3</sub>, -NHSO<sub>2</sub>CF<sub>3</sub>, halogen, -CF<sub>3</sub>, OH, -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(O)NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>R<sub>32</sub>, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkoxy, aminoalkoxy, NH(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy, N(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy,

wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub>

alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, and benzyl wherein the phenyl group is unsubstituted or substituted with 1 or 2 groups that are independently methoxy, ethoxy, or halogen, or

5 wherein at each occurrence R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, or piperidinyl ring each of which is optionally substituted with hydroxy, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or-  
10 C(O)NH<sub>2</sub>.

More preferred compounds include those wherein  
R<sub>35</sub> is 3-fluoro, 5-benzyloxyphenyl or 3-chloro, 5-benzyloxyphenyl.

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More preferred compounds include those wherein  
R<sub>35</sub> is -S-phenyl, benzo[1,3]dioxole, furanyl, or thienyl;  
R<sub>41</sub> is H, cyclohexyl, phenyl, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy,  
20 or C<sub>1</sub>-C<sub>4</sub> thioalkoxy; and  
R<sub>42</sub> is hydrogen or -CH<sub>2</sub>CN.

More preferred compounds include those wherein  
R<sub>40</sub> is phenyl, -phenyl-pyridine, biphenyl, -phenyl-pyrimidinyl,  
25 -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-C(O)NH-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-C(O)O-(C<sub>1</sub>-C<sub>4</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>33</sub>, or C<sub>1</sub>-C<sub>8</sub> alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that  
30 are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, -Obenzyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, or -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), -NHSO<sub>2</sub>CF<sub>3</sub>.

Still more preferred compounds include those wherein

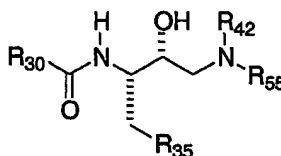
- R<sub>40</sub> is phenyl or C<sub>1</sub>-C<sub>8</sub> alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, -Obenzyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, or -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); and
- R<sub>41</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or C<sub>1</sub>-C<sub>4</sub> thioalkoxy; and;
- R<sub>42</sub> is hydrogen; and
- R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl) wherein the alkyl group is optionally substituted with 1, 2, or 3 halogens, -SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH<sub>2</sub>, -SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>1</sub>-C<sub>4</sub> alkyl), -NHC(O)NH<sub>2</sub>, -NHC(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -NHC(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)NH<sub>2</sub>, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), halogen, -CF<sub>3</sub>, OH, -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(O)NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>R<sub>32</sub>, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl, -Obenzyl, -NHC(S)NH<sub>2</sub>, -NHC(S)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -NHC(S)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), (C<sub>1</sub>-C<sub>4</sub> alkyl)-O-phenyl, -C(O)-(C<sub>1</sub>-C<sub>6</sub> alkyl), -O-cyclopentyl, -O-cyclohexyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkoxy, aminoalkoxy, NH(C<sub>1</sub>-C<sub>6</sub> alkyl)-alkoxy, N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl)-alkoxy,
- wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), and benzyl wherein the phenyl group is unsubstituted or substituted with 1, or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkoxy, or halogen,
- wherein at each occurrence R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, or piperidinyl, each of

which is optionally substituted with hydroxy, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NH<sub>2</sub>, or -C(O)NH-benzyl.

- 5 Still more preferred compounds include those wherein  
 R<sub>40</sub> is phenyl or C<sub>1</sub>-C<sub>8</sub> alkyl, wherein each of the above is  
 unsubstituted or substituted with 1, 2, or 3 groups that  
 are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or  
 CF<sub>3</sub>; and  
 10 R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
 alkoxy, -NHSO<sub>2</sub>CH<sub>3</sub>, -NHSO<sub>2</sub>CF<sub>3</sub>, halogen, -CF<sub>3</sub>, OH,  
 -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(O)NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>R<sub>32</sub>, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl,  
 hydroxy C<sub>1</sub>-C<sub>4</sub> alkoxy, aminoalkoxy, NH(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy,  
 N(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy,  
 15 wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently  
 selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub>  
 alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, and benzyl wherein the  
 phenyl group is unsubstituted or substituted with 1  
 or 2 groups that are independently methoxy, ethoxy,  
 20 or halogen, or  
 wherein at each occurrence R<sub>31</sub>, R<sub>32</sub> and the nitrogen to  
 which they are attached independently form a  
 pyrrolidinyl, piperazinyl, or piperidinyl ring each  
 of which is optionally substituted with hydroxy,  
 25 hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or-  
 C(O)NH<sub>2</sub>.

Particularly preferred compounds of Formula X are those  
 where R<sub>1</sub> is 3,5-difluorophenyl.

- 30 In another specific aspect within Formula X, the invention  
 provides compounds of formula Z3



## Z3

or a pharmaceutically acceptable salt thereof, wherein

R<sub>30</sub> is selected from the group consisting of phenyl, pyrazolopyrimidinyl, oxa-aza-benzoazulenyl, isoxazolyl, triazolopyridinyl, pyrrolidinonyl, tetrahydrothia-aza-fluorenyl, pyridyl, piperidinyl, dihydrocyclopentaquinolinyl, furyl, naphthothienyl, phthalazinonyl, thiadiazolyl, thienopyrimidinonyl, oxa-diaza-cyclopentanaphthalenyl, dihydrobenzodioxepinyl, chromanonyl, chromenonyl, oxazolidinyl, purinyl, oxazolyl, thiazolyl, pyridazinonyl, thiazolyl, pyranyl, dihydropyranopyridinyl, diazepanyl, cyclopropyl, dihydronaphthoisoxazolyl, benzoindazole, dihydrocyclopentachromenonyl, imidazopyrazolyl, tetrahydrocyclopentachromenonyl, dihydroquinolinonyl, pyridyl, isochromanlyl, quinazolinonyl, pyrazolopyridinyl, dihydrobenzothiophene dioxide, dihydrofurobenzoisoxazolyl, dihydropyrimidine dionyl, thienopyrazolyl, oxazolyl, tetrahydrocyclopentapyrazolyl, dihydronaphthalenonyl, dihydrobenzofuranonyl, dihydrocyclopentathienyl, tetrahydrocyclopentapyrazolyl, tetrahydropyrazoloazepinyl, indazolyl, tetrahydrocycloheptaisoxazolyl, tetrahydroindolonyl, pyrrolidinyl, thienopyridinyl, dioxodihydrobenzoisothiazolonyl, triazolopyrimidinyl, thienyl, dihydrothienopyrimidinonyl, and benzooxadiazolyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently selected from the group consisting of C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with phenyl, hydroxy, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with phenyl or (C<sub>1</sub>-C<sub>4</sub> alkyl)phenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy optionally substituted with 1 or 2 hydroxy groups, -C(O)NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl) wherein the alkyl group is optionally substituted with 1, 2, or 3 R<sub>33</sub> groups, -

SO<sub>2</sub>-NH(C<sub>1</sub>-C<sub>6</sub> alkyl) wherein the alkyl group is optionally substituted with 1 or 2 R<sub>33</sub> groups, -SO<sub>2</sub>-N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl) wherein each alkyl group is optionally substituted with 1 or 2 R<sub>33</sub> groups, -SO<sub>2</sub>-NH(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl wherein the phenyl is optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkoxy or halogen, -O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-phenyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, triazolidine-3,5-dione, halogen, -NHC(O)NH<sub>2</sub>, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)NH<sub>2</sub>, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)thienyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl) furanyl, -S-(C<sub>1</sub>-C<sub>6</sub> alkyl)phenyl, -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(O)-NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>R<sub>32</sub>, dithiane, -NHC(S)NH<sub>2</sub>, -NHC(S)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -NHC(S)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -CO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), tetrahydropyran, phenyl optionally substituted with 1 or 2 groups that are independently F, Cl or Br, pyridine, -C<sub>2</sub>-C<sub>4</sub> alkynyl-phenyl, -O-C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-R<sub>33</sub>, benzo[1,2,5]oxadiazole, -C(O)-(C<sub>1</sub>-C<sub>6</sub> alkyl) wherein the alkyl group is optionally substituted with NH<sub>2</sub>, N(C<sub>1</sub>-C<sub>6</sub> alkyl), or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); -C(O)NH-phenyl, -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, 4,4-Dimethyl-4,5-dihydro-oxazole, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-S-pyridine, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-SO<sub>2</sub>-pyridine, -(C<sub>1</sub>-C<sub>6</sub> thioalkoxy)-pyridine,

wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(O)NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub>

- alkyl)phenyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)pyridyl, -C(O)furanyl, (C<sub>1</sub>-C<sub>6</sub> alkyl)-tetrahydrofuran, wherein the phenyl and pyridyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or
- R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or a 6 membered heteroaryl ring, each of which is optionally fused to a benzene, pyridine or pyrimidine ring and each of which is optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkoxy, hydroxy, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NH<sub>2</sub>, -C(O)NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, ;
- R<sub>33</sub> at each occurrence is independently, H, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(phenyl);
- R<sub>35</sub> is phenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -S-phenyl, benzodioxole, thienyl, C<sub>1</sub>-C<sub>6</sub> alkyl, furanyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>5</sub>-C<sub>6</sub> cycloalkyl);
- R<sub>42</sub> is H, C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl, -NHC(O)-(C<sub>1</sub>-C<sub>6</sub> alkyl), or -NHC(O)-phenyl wherein the phenyl is optionally substituted with 1 or 2 alkyl groups,
- R<sub>55</sub> is cyclohexyl; cyclopentyl; azepanone; phenyl; piperidinyl; -SO<sub>2</sub>-phenyl; pyrrolidinyl; or 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine; wherein each is optionally substituted with -C(O)NH<sub>2</sub>; -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl); -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl; -O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(O)NR<sub>31</sub>R<sub>32</sub>; -(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl; 4,5-dihydro-2H-pyridazin-3-one; C<sub>5</sub>-C<sub>6</sub> cycloalkyl which is optionally substituted with one CN group, phenyloxy wherein the

phenyl group is optionally substituted with  $-\text{NHC}(\text{O})\text{C}_1\text{-C}_6$  alkyl,  $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{C}(\text{O})\text{C}_1\text{-C}_6 \text{ alkyl}$ , wherein

$\text{R}_{31}$ ,  $\text{R}_{32}$  and the nitrogen to which they are attached form a pyrrolidine, piperidine, piperazine, morpholine, or thiamorpholine ring, wherein each ring is unsubstituted or substituted with 1, 2, or 3 groups that are independently OH,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  alkoxy,  $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-imidazole}$  wherein the imidazole is optionally substituted with 1 or 2  $\text{C}_1\text{-C}_4$  alkyl groups, or hydroxy  $(\text{C}_1\text{-C}_6 \text{ alkyl})$  wherein the alkyl group is optionally substituted with 1 phenyl ring,

or

$\text{R}_{42}$ ,  $\text{R}_{55}$  and the nitrogen to which they are attached form a tetrahydroisoquinolinyl, dihydroisoquinolinyl, or isoquinolinyl group which is optionally substituted by 1, 2, 3, or 4 groups that are independently halogen,  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_1\text{-C}_4$  alkoxy, CN, OH, and phenyl, wherein the phenyl is optionally substituted with halogen, hydroxyl,  $\text{C}_1\text{-C}_4$  alkoxy, and  $\text{C}_1\text{-C}_4$  alkyl.

More preferred compounds of Z3 include those wherein

$\text{R}_{30}$  is selected from the group consisting of phenyl, pyrrolidinonyl, pyridyl, piperidinyl, furyl, cyclopropyl, and thienyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently selected from the group consisting of  $\text{C}_1\text{-C}_{10}$  alkyl, hydroxy, hydroxy  $\text{C}_1\text{-C}_{10}$  alkyl  $\text{C}_1\text{-C}_6$  alkoxy,  $-\text{NR}_{31}\text{-SO}_2\text{-(C}_1\text{-C}_6 \text{ alkyl)}$ ,  $-\text{SO}_2\text{-NH(C}_1\text{-C}_6 \text{ alkyl)}$ ,  $-\text{SO}_2\text{-N(C}_1\text{-C}_6 \text{ alkyl)(C}_1\text{-C}_6 \text{ alkyl)}$ , halogen,  $-\text{NHC}(\text{O})\text{NH}_2$ ,  $-\text{N(C}_1\text{-C}_6 \text{ alkyl)C}(\text{O})\text{NH}_2$ ,  $-\text{N(C}_1\text{-C}_6 \text{ alkyl)C}(\text{O})\text{NH(C}_1\text{-C}_6 \text{ alkyl)}$ ,  $-\text{N(C}_1\text{-C}_6 \text{ alkyl)C}(\text{O})\text{N(C}_1\text{-C}_6 \text{ alkyl)(C}_1\text{-C}_6 \text{ alkyl)}$ ,  $-\text{SO}_2\text{NR}_{31}\text{R}_{32}$ ,  $-\text{C}(\text{O})-\text{NR}_{31}\text{R}_{32}$ ,  $-\text{NR}_{31}\text{R}_{32}$ ,  $-\text{C}_2\text{-C}_4$  alkynyl-phenyl,  $-\text{O-C}_3\text{-C}_6$  cycloalkyl,  $-\text{O-(C}_1\text{-C}_6 \text{ alkyl)-R}_{33}$ , benzo[1,2,5]oxadiazole,  $-\text{C}(\text{O})\text{-(C}_1\text{-C}_6 \text{ alkyl)}$ ;



wherein  $R_{31}$  and  $R_{32}$  at each occurrence are independently selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl, hydroxy  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $-(C_1-C_6 \text{ alkyl})-C(O)NH_2$ ,  $-(C_1-C_6 \text{ alkyl})-C(O)NH(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_6 \text{ alkyl})-C(O)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_6 \text{ alkyl})-NH_2$ ,  $-(C_1-C_6 \text{ alkyl})-NH(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_6 \text{ alkyl})-N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ , benzyl, and  $-C(O)furanyl$ , wherein

the phenyl and pyridyl groups are unsubstituted or substituted with 1, 2, or 3, groups that are independently  $C_1$ - $C_4$  alkyl, hydroxy,  $C_1$ - $C_4$  alkoxy, or halogen, or

$R_{31}$ ,  $R_{32}$  and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or a 6 membered heteroaryl ring, each of which is optionally substituted with  $C_1$ - $C_6$  alkoxy, hydroxy, hydroxy  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_4$  alkoxy  $C_1$ - $C_6$  alkyl, or  $-C(O)NH_2$ ;

$R_{35}$  is phenyl,  $C_3$ - $C_6$  cycloalkyl, or  $-S$ -phenyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $CF_3$ ,  $OCF_3$ , halogen,  $-Obenzyl$ ,  $-CO_2-(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_4 \text{ alkyl})-(C_5-C_6 \text{ cycloalkyl})$ ;

$R_{42}$  is H,  $C_1$ - $C_6$  alkyl, benzyl,  $-NHC(O)-(C_1-C_6 \text{ alkyl})$ , or  $-NHC(O)$ -phenyl wherein the phenyl is optionally substituted with 1 or 2 alkyl groups,

$R_{55}$  is cyclohexyl; azepanone; phenyl; piperidinyl;  $-SO_2$ -phenyl; pyrrolidinyl; or 4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine; wherein each is optionally substituted with  $-C(O)NH_2$ ;  $C_1$ - $C_6$  alkoxycarbonyl;  $-O-(C_1-C_6 \text{ alkyl})-C(O)NR_{31}R_{32}$ ;  $-(C_1-C_6 \text{ alkyl})$ -phenyl; 4,5-dihydro-2H-pyridazin-3-one; cyclopentyl which is optionally substituted with one CN group, phenyloxy wherein the phenyl group is optionally substituted with  $-NHC(O)C_1-C_6 \text{ alkyl}$ , wherein

5 R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached form a pyrrolidine, piperidine, piperazine, or morpholine ring, wherein each ring is unsubstituted or substituted with 1, 2, or 3 groups that are independently OH, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-imidazole wherein the imidazole is optionally substituted with 1 or 2 C<sub>1</sub>-C<sub>4</sub> alkyl groups, or hydroxy (C<sub>1</sub>-C<sub>6</sub> alkyl) wherein the alkyl group is optionally substituted with 1 phenyl ring,

10 or

R<sub>42</sub>, R<sub>55</sub> and the nitrogen to which they are attached form a tetrahydroisoquinolinyl, group which is optionally substituted by 1, 2, 3, or 4 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CN, OH, and phenyl, wherein the phenyl is optionally substituted with halogen, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, and C<sub>1</sub>-C<sub>4</sub> alkyl.

Even more preferred compounds of Z3 include those wherein R<sub>30</sub> is selected from the group consisting of phenyl, pyridyl, or piperidinyl wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently selected from the group consisting of C<sub>1</sub>-C<sub>10</sub> alkyl, hydroxy, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(O) -NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>R<sub>32</sub>, -O-C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -C(O)-(C<sub>1</sub>-C<sub>6</sub> alkyl);

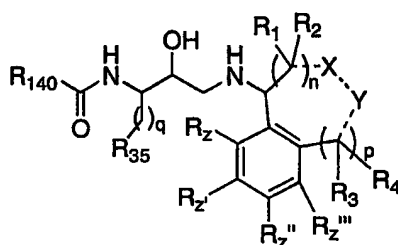
25 wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), benzyl, and -C(O)furanyl, wherein

30 the phenyl group is unsubstituted or substituted with 1, 2, or 3, groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, or halogen, or

R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached form a pyrrolidinyl, piperidinyl, morpholinyl, pyridinyl, or pyrimidinyl ring, each of which is optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkoxy, hydroxy, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NH<sub>2</sub>;

R<sub>35</sub> is phenyl, cyclohexyl, cyclopentyl, or -S-phenyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, OCF<sub>3</sub>, halogen, -Obenzyl, -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>5</sub>-C<sub>6</sub> cycloalkyl).

In a specific aspect, the invention provides compounds of formula X100:



**X100**

and the pharmaceutically acceptable salts thereof, wherein n, p, and q are independently 0, 1 or 2; a dashed line res a single or double bond; R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are independently selected from

hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo(C<sub>1</sub>-C<sub>6</sub>) alkyl, hydroxy(C<sub>1</sub>-C<sub>6</sub>) alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy, thio(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl,

-(CH<sub>2</sub>)<sub>0-4</sub>-aryl or -(CH<sub>2</sub>)<sub>0-4</sub>-heteroaryl, C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl, each of which is optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, hydroxy, -SH, cyano, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy,

- amino, mono (C<sub>1</sub>-C<sub>6</sub>)alkylamino, and di(C<sub>1</sub>-C<sub>6</sub>)alkylamino,
- 5      -(CH<sub>2</sub>)<sub>0-4</sub>- C<sub>3</sub>-C<sub>7</sub> cycloalkyl, where the cycloalkyl is optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, hydroxy, -SH, cyano, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, and di(C<sub>1</sub>-C<sub>6</sub>)alkylamino;
- 10      R<sub>z</sub>, R<sub>z</sub>', R<sub>z</sub>'', and R<sub>z</sub>''' independently re C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with one, two or three substituents independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, and di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, hydroxy, nitro, halogen, -CO<sub>2</sub>H, cyano,
- 15      -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>142</sub>R<sub>144</sub> where R<sub>142</sub> and R<sub>144</sub> independently re hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, haloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>2</sub> alkyl)-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), -C<sub>2</sub>-C<sub>6</sub> alkenyl with one or two double bonds, -C<sub>2</sub>-C<sub>6</sub> alkynyl with one or two triple bonds, -C<sub>1</sub>-C<sub>6</sub> alkyl chain with one double bond and one triple bond, -R<sub>1</sub>-aryl where R<sub>1</sub>-aryl is as defined above, or -R<sub>1</sub>-heteroaryl where R<sub>1</sub>-heteroaryl,
- 20      -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>1</sub>-C<sub>12</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub> alkenyl),
- 25      (CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub>)alkynyl, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>1</sub>-aryl where R<sub>1</sub>-aryl is as defined above, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>1</sub>-heteroaryl where R<sub>1</sub>-heteroaryl is as defined above, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>1</sub>-heterocycle, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>146</sub> where R<sub>146</sub> is heterocycloalkyl, where the
- 30      heterocycloalkyl is optionally substituted with 1-4 of C<sub>1</sub>-C<sub>6</sub> alkyl,
- (CH<sub>2</sub>)<sub>0-4</sub>-CO-O-R<sub>148</sub> where R<sub>148</sub> is selected from the group consisting of: C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-(R<sub>1</sub>-aryl), C<sub>2</sub>-C<sub>6</sub>

- alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and -(CH<sub>2</sub>)<sub>0-2</sub>-(R<sub>1</sub>-heteroaryl),
- 5 -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-N R<sub>142</sub>R<sub>144</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-SO-(C<sub>1</sub>-C<sub>8</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>12</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>148</sub>)-CO-O-R<sub>148</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>148</sub>)-CO-N(R<sub>148</sub>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N-CS-N(R<sub>148</sub>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(-H or R<sub>148</sub>)-CO-R<sub>142</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-NR<sub>142</sub>R<sub>144</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>146</sub> where R<sub>N-4</sub> is as defined above,
- 10 -(CH<sub>2</sub>)<sub>0-4</sub>-O-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-O-P(O)-(OR<sub>150</sub>)<sub>2</sub> where each R<sub>150</sub> is independently hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl, -(CH<sub>2</sub>)<sub>0-4</sub>-O-CO-N(R<sub>148</sub>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-O-CS-N(R<sub>148</sub>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-O-(R<sub>148</sub>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-O-(R<sub>148</sub>)<sub>2</sub>-CO<sub>2</sub>H, -(CH<sub>2</sub>)<sub>0-4</sub>-S-(R<sub>148</sub>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-O-halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, -(CH<sub>2</sub>)<sub>0-4</sub>-O-(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl,
- 15 C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl, each of which is optionally substituted with C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, hydroxy, -SH, cyano, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, and di(C<sub>1</sub>-C<sub>6</sub>)alkylamino,
- 20 -(CH<sub>2</sub>)<sub>0-4</sub>-N(-H or R<sub>148</sub>)-SO<sub>2</sub>-R<sub>142</sub>, or -(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>7</sub> cycloalkyl;
- R<sub>35</sub> is phenyl, cyclohexyl, -S-phenyl, benzodioxole, thienyl, C<sub>3</sub>-C<sub>6</sub> alkyl, furanyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), or -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>5</sub>-C<sub>6</sub> cycloalkyl);
- 25 X and Y are independently selected from O, NR<sub>5</sub>, C(O), CR<sub>1</sub>R<sub>2</sub>, SO<sub>2</sub>, and S,
- 30 where R<sub>5</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, SO<sub>2</sub>R<sub>5'</sub>, C(O)R<sub>5'</sub> where R<sub>5'</sub> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo(C<sub>1</sub>-C<sub>6</sub>) alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy, thio(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl,

mono (C<sub>1</sub>-C<sub>6</sub>) alkylamino (C<sub>1</sub>-C<sub>6</sub>) alkyl, di (C<sub>1</sub>-  
 C<sub>6</sub>) alkylamino (C<sub>1</sub>-C<sub>6</sub>) alkyl,  
 -(CH<sub>2</sub>)<sub>0-4</sub>-aryl or -(CH<sub>2</sub>)<sub>0-4</sub>-heteroaryl,  
 C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl, each of which is optionally  
 5 substituted with one, two or three substituents  
 independently selected from the group consisting of  
 halogen, hydroxy, -SH, cyano, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy,  
 amino, mono (C<sub>1</sub>-C<sub>6</sub>) alkylamino, and di (C<sub>1</sub>-  
 C<sub>6</sub>) alkylamino,  
 10 -(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>7</sub> cycloalkyl, where the cycloalkyl is  
 optionally substituted with one, two or three  
 substituents independently selected from the group  
 consisting of halogen, hydroxy, -SH, cyano, -CF<sub>3</sub>, C<sub>1</sub>-  
 C<sub>3</sub> alkoxy, amino, mono (C<sub>1</sub>-C<sub>6</sub>) alkylamino, and di (C<sub>1</sub>-  
 15 C<sub>6</sub>) alkylamino;  
 R<sub>140</sub> res phenyl or naphthyl, each of which is optionally  
 substituted with 1-5 groups independently selected from  
 C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with one, two or three  
 substituents selected from the group consisting of  
 20 C<sub>1</sub>-C<sub>3</sub> alkyl, -halogen, hydroxy, -SH, cyano, -CF<sub>3</sub>, C<sub>1</sub>-  
 C<sub>3</sub> alkoxy, amino, mono (C<sub>1</sub>-C<sub>6</sub>) alkylamino, and di (C<sub>1</sub>-  
 C<sub>6</sub>) alkylamino,  
 hydroxy, nitro, halogen, -CO<sub>2</sub>H, cyano,  
 -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>142</sub>R<sub>144</sub> where R<sub>142</sub> and R<sub>144</sub> independently re  
 25 hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxyl (C<sub>1</sub>-C<sub>6</sub>) alkyl, amino (C<sub>1</sub>-  
 C<sub>6</sub>) alkyl, haloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>2</sub> alkyl)-  
 (C<sub>3</sub>-C<sub>7</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), -  
 C<sub>2</sub>-C<sub>6</sub> alkenyl with one or two double bonds, -C<sub>2</sub>-C<sub>6</sub>  
 alkynyl with one or two triple bonds, -C<sub>1</sub>-C<sub>6</sub> alkyl  
 30 chain with one double bond and one triple bond, -R<sub>1</sub>-  
 aryl where R<sub>1</sub>-aryl is as defined above, or -R<sub>1</sub>-heteroaryl  
 where R<sub>1</sub>-heteroaryl,  
 -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>1</sub>-C<sub>12</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub> alkenyl),  
 (CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub>) alkynyl, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>3</sub>-C<sub>7</sub>

cycloalkyl),  $-(CH_2)_{0-4}-CO-R_1\text{-aryl}$  where  $R_1\text{-aryl}$  is as defined above,  $-(CH_2)_{0-4}-CO-R_1\text{-heteroaryl}$  where  $R_1\text{-heteroaryl}$  is as defined above,  $-(CH_2)_{0-4}-CO-R_1\text{-heterocycle}$ ,  $-(CH_2)_{0-4}-CO-R_{146}$  where  $R_{146}$  is heterocycloalkyl, where the heterocycloalkyl is optionally substituted with 1-4 of  $C_1-C_6$  alkyl,

5  $-(CH_2)_{0-4}-CO-O-R_{148}$  where  $R_{148}$  is selected from the group consisting of:  $C_1-C_6$  alkyl,  $-(CH_2)_{0-2}-(R_1\text{-aryl})$ ,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl,  $C_3-C_7$  cycloalkyl, and  $-(CH_2)_{0-2}-(R_1\text{-heteroaryl})$ ,

10  $-(CH_2)_{0-4}-SO_2-N R_{142}R_{144}$ ,  $-(CH_2)_{0-4}-SO-(C_1-C_8 \text{ alkyl})$ ,  $-(CH_2)_{0-4}-SO_2-(C_1-C_{12} \text{ alkyl})$ ,  $-(CH_2)_{0-4}-SO_2-(C_3-C_7 \text{ cycloalkyl})$ ,  $-(CH_2)_{0-4}-N(H \text{ or } R_{148})-CO-O-R_{148}$ ,  $-(CH_2)_{0-4}-N(H \text{ or } R_{148})-CO-N(R_{148})_2$ ,  $-(CH_2)_{0-4}-N-CS-N(R_{148})_2$ ,  $-(CH_2)_{0-4}-N(-H \text{ or } R_{148})-CO-R_{142}$ ,  $-(CH_2)_{0-4}-NR_{142}R_{144}$ ,  $-(CH_2)_{0-4}-R_{146}$  where  $R_{N-4}$  is as defined above,

15  $-(CH_2)_{0-4}-O-CO-(C_1-C_6 \text{ alkyl})$ ,  $-(CH_2)_{0-4}-O-P(O)-(OR_{150})_2$  where each  $R_{150}$  is independently hydrogen or  $C_1-C_4$  alkyl,  $-(CH_2)_{0-4}-O-CO-N(R_{148})_2$ ,  $-(CH_2)_{0-4}-O-CS-N(R_{148})_2$ ,  $-(CH_2)_{0-4}-O-(R_{148})_2$ ,  $-(CH_2)_{0-4}-O-(R_{148})_2-CO_2H$ ,  $-(CH_2)_{0-4}-S-(R_{148})_2$ ,  $-(CH_2)_{0-4}-O\text{-halo}(C_1-C_6)\text{alkyl}$ ,  $-(CH_2)_{0-4}-O-(C_1-C_6)\text{alkyl}$ ,  $C_3-C_7$  cycloalkyl,

20  $C_2-C_6$  alkenyl or  $C_2-C_6$  alkynyl, each of which is optionally substituted with  $C_1-C_3$  alkyl, halogen, hydroxy,  $-SH$ , cyano,  $-CF_3$ ,  $C_1-C_3$  alkoxy, amino, mono( $C_1-C_6$ )alkylamino, and di( $C_1-C_6$ )alkylamino, and

25  $-(CH_2)_{0-4}-N(-H \text{ or } R_{148})-SO_2-R_{142}$ , or  $-(CH_2)_{0-4}-C_3-C_7$  cycloalkyl.

30 In a more preferred embodiment  $q$  is 1.

In a more preferred embodiment, two or three of  $R_z$ ,  $R_z'$ ,  $R_z''$ , and  $R_z'''$  is hydrogen, and

the other one or two of  $R_z$ ,  $R_z'$ ,  $R_z''$ , and  $R_z'''$  is hydroxy, nitro, halogen,  $-\text{CO}_2\text{H}$ , cyano, or  $\text{C}_1\text{-C}_6$  alkyl, where the alkyl is optionally substituted with one, two or three substituents independently selected from  $\text{C}_1\text{-C}_3$  alkyl, halogen,  $-\text{OH}$ ,  $-\text{SH}$ ,  $-\text{C}\equiv\text{N}$ ,  $-\text{CF}_3$ ,  $\text{C}_1\text{-C}_6$  alkoxy, amino, mono( $\text{C}_1\text{-C}_6$ )alkylamino, and di( $\text{C}_1\text{-C}_6$ )alkylamino.

Preferred compounds of formula X100 include those where three of  $R_z$ ,  $R_z'$ ,  $R_z''$ , and  $R_z'''$  are hydrogen and the other is ( $\text{C}_1\text{-C}_6$ )alkyl, halogen, or ( $\text{C}_1\text{-C}_6$ )alkoxy.

Other preferred compounds of formula X100 include those where wherein  $R_{140}$  is phenyl substituted with 1, 2, or 3 groups independently selected from  $\text{C}_1\text{-C}_6$  alkyl, optionally substituted with one, two or three groups independently selected from  $\text{C}_1\text{-C}_3$  alkyl, halogen, hydroxy,  $-\text{SH}$ , cyano,  $-\text{CF}_3$ ,  $\text{C}_1\text{-C}_3$  alkoxy, amino, mono( $\text{C}_1\text{-C}_6$ )alkylamino, and di( $\text{C}_1\text{-C}_6$ )alkylamino, hydroxy, nitro, halogen,  $-\text{CO}_2\text{H}$ , cyano,  $-(\text{CH}_2)_{0-4}\text{-CO-NR}_{142}\text{R}_{144}$  where  $R_{142}$  and  $R_{144}$  independently are hydrogen,  $\text{C}_1\text{-C}_6$  alkyl, hydroxy( $\text{C}_1\text{-C}_6$ )alkyl, amino( $\text{C}_1\text{-C}_6$ )alkyl, and  $\text{C}_3\text{-C}_7$  cycloalkyl.

Still other preferred compounds of formula X100 include those where  $R_{140}$  is phenyl substituted with one of hydroxy, nitro, halogen,  $-\text{CO}_2\text{H}$ , cyano, or  $\text{C}_1\text{-C}_6$  alkyl where the alkyl is optionally substituted with one, two or three groups independently selected from  $\text{C}_1\text{-C}_3$  alkyl, halogen, hydroxy,  $-\text{SH}$ , cyano,  $-\text{CF}_3$ ,  $\text{C}_1\text{-C}_3$  alkoxy, amino, mono( $\text{C}_1\text{-C}_6$ )alkylamino, and di( $\text{C}_1\text{-C}_6$ )alkylamino; and one of  $-(\text{CH}_2)_{0-4}\text{-CO-NR}_{142}\text{R}_{144}$ .



Other preferred compounds of formula X100 are those where  $R_{140}$  is phenyl substituted with one of  $-C(O)NR_{142}R_{144}$  and  $R_{142}$  and  $R_{144}$  are independently hydrogen or  $C_1$ - $C_6$  alkyl.

5 More preferred compounds of formula X100 include those where  $R_{142}$  and  $R_{144}$  are the same and are propyl.

Other specific compounds of formula X100 include those where  $R_{35}$  is phenyl substituted with 1-5 halogen, or  
10 substituted with 1, 2, or 3 groups independently selected from  $(C_1-C_6)$  alkyl, hydroxy, halogen,  $(C_1-C_6)$ alkoxy, amino, mono( $C_1-C_6$ )alkylamino, and di( $C_1-C_6$ )alkylamino.

Preferred compounds of formula X100 include those where  
15  $R_{35}$  is phenyl substituted with 2 halogens.

Still other preferred compounds of formula X100 are those where  $R_{35}$  is 3,5-difluorophenyl.

20 Other specific compounds of formula X100 include those where  $R_{140}$  is phenyl substituted with one of hydroxy, nitro, halogen,  $-CO_2H$ , cyano, or  $C_1-C_6$  alkyl where the alkyl is optionally substituted with one, two or three groups independently selected from  $C_1-C_3$  alkyl, -  
25 halogen, hydroxy,  $-SH$ , cyano,  $-CF_3$ ,  $C_1-C_3$  alkoxy, amino, mono( $C_1-C_6$ )alkylamino, and di( $C_1-C_6$ )alkylamino; and one of  $-(CH_2)_{0-4}-CO-NR_{142}R_{144}$ .

Preferred specific compounds of formula X100 are those  
30 where  $R_{140}$  is phenyl substituted with one of  $-C(O)NR_{142}R_{144}$  and  $R_{142}$  and  $R_{144}$  are independently hydrogen or  $C_1-C_6$  alkyl.

Other preferred specific compounds of formula X100 are those where  $R_{142}$  and  $R_{144}$  are the same and are propyl.

Preferred compounds of formula X100 are those where n is 1 and p is 0.

Still other preferred compounds of formula X100 are those  
5 where the dashed lines all re single bonds.

In other preferred compounds of formula X100, R<sub>1</sub> is hydrogen and X is SO<sub>2</sub>.

In other preferred compounds of Z100, Y is methylene.

More preferred compounds of X100 are those where Z' is 2-  
10 propyl.

Other more preferred compounds of X100 are those where Y is methylene and R<sub>2</sub> is hydrogen, hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl, or (C<sub>1</sub>-C<sub>3</sub>)alkyl.

A preferred R<sub>2</sub> group is methyl.

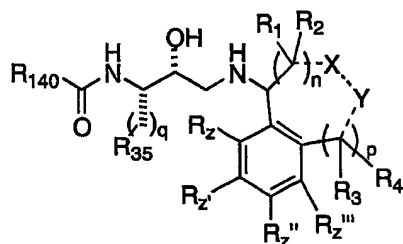
15           In another specific aspect of formula X100, R<sub>1</sub> is  
hydrogen;

X is SO<sub>2</sub> and Y is NR<sub>5</sub>, or X is NR<sub>5</sub> and Y is SO<sub>2</sub>, where each R<sub>5</sub> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, or hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl.

In a preferred aspect of X100,  
20 R<sub>1</sub> is hydrogen;

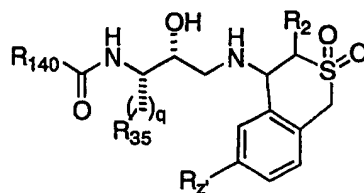
X is C(O) and Y is NR<sub>5</sub>, or X is NR<sub>5</sub> and Y is C(O), where each R<sub>5</sub> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, or hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl.

Preferred compounds of formula X100 include those of formula X101

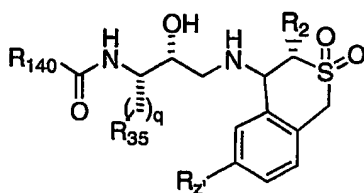


X101.

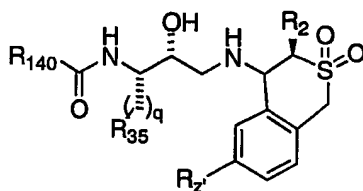
Other preferred compounds of formula X100 include those of formula X102

X102.

Preferred compounds of formula X100 include those of  
5 formula X103

103.

Other preferred compounds of formula X100 include those of  
10 formula X104

104.

Preferred compounds of formula X103 include those wherein  
15 R<sub>2</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkyl.

Other preferred compounds of formula X103 include those wherein R<sub>2</sub> is methyl.

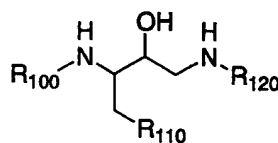
Still other preferred compounds of formula X103 include those wherein R<sub>2</sub> is hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl.

20 Preferred compounds of formula X104 include those wherein R<sub>2</sub> is (C<sub>1</sub>-C<sub>3</sub>)alkyl.

Other preferred compounds of formula X104 include those wherein R<sub>2</sub> is methyl.

Still other preferred compounds of formula X104 include those wherein  $R_2$  is hydroxy( $C_1$ - $C_3$ )alkyl.

In a specific aspect, the invention provides compounds of the formula Z4:



Z4

wherein

$R_{100}$  is H,  $C_1$ - $C_8$  alkoxy carbonyl, phenyl  $C_1$ - $C_6$  alkyl, or phenyl  $C_1$ - $C_6$  alkoxy carbonyl;

$R_{110}$  is phenyl  $C_1$ - $C_6$  alkyl, thienyl, -S-phenyl, furanyl, or benzodioxolyl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, or phenyl  $C_1$ - $C_6$  alkoxy; and

$R_{120}$  is H, phenyl  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_8$  cycloalkyl optionally substituted with  $C_1$ - $C_6$  alkyl or phenyl,  $C_3$ - $C_8$  cycloalkyl  $C_1$ - $C_4$  alkyl, or  $C_1$ - $C_6$  alkyl optionally substituted with  $-C(O)NR_{121}R_{122}$ , wherein each of the above is optionally substituted with 1, 2, or 3 groups that are independently  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl, halogen, or  $C_1$ - $C_6$  alkoxy; wherein

$R_{121}$  and  $R_{122}$  are independently H, or  $C_1$ - $C_6$  alkyl.

More preferred compound of Z4 include those wherein  $R_{100}$  is tertiary butoxy carbonyl.

More preferred compound of Z4 include those wherein  $R_{110}$  is phenyl  $C_1$ - $C_6$  alkyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, or phenyl  $C_1$ - $C_6$  alkoxy.

More preferred compound of Z4 include those wherein  $R_{110}$  is monohalophenyl, dihalophenyl, or trihalophenyl.

More preferred compound of Z4 include those wherein  $R_{110}$  is thienyl, or -S-phenyl each of which is optionally substituted

with 1, 2, 3, 4, or 5 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, benzyloxy.

More preferred compound of Z4 include those wherein R<sub>110</sub> is furanyl, or benzodioxolyl each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, benzyloxy.

More preferred compound of Z4 include those wherein R<sub>120</sub> is benzyl optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, or C<sub>1</sub>-C<sub>6</sub> alkoxy.

More preferred compound of Z4 include those wherein R<sub>120</sub> is cyclopropyl optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl; or cyclopropyl C<sub>1</sub>-C<sub>4</sub> alkyl, wherein each of the above is optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, or C<sub>1</sub>-C<sub>6</sub> alkoxy.

Even more preferred compound of Z4 include those wherein R<sub>110</sub> is phenyl C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or phenyl C<sub>1</sub>-C<sub>6</sub> alkoxy; and R<sub>120</sub> is H or benzyl optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, or C<sub>1</sub>-C<sub>6</sub> alkoxy.

Other even more preferred compound of Z4 include those wherein

R<sub>110</sub> is phenyl C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or phenyl C<sub>1</sub>-C<sub>6</sub> alkoxy; and

R<sub>120</sub> is cyclopropyl optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl; or cyclopropyl C<sub>1</sub>-C<sub>4</sub> alkyl, wherein each of the above is optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, or C<sub>1</sub>-C<sub>6</sub> alkoxy.

Other even more preferred compound of Z4 include those wherein

- 5     R<sub>110</sub> is thienyl, or -S-phenyl each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, benzyloxy; and
- 10     R<sub>120</sub> is H or benzyl optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, or C<sub>1</sub>-C<sub>6</sub> alkoxy.

Other even more preferred compound of Z4 include those wherein

- 15     R<sub>110</sub> is thienyl, or -S-phenyl each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, benzyloxy; and
- 20     R<sub>120</sub> is cyclopropyl optionally substituted with C<sub>1</sub>-C<sub>6</sub> alky or phenyl; or cyclopropyl C<sub>1</sub>-C<sub>4</sub> alkyl, wherein each of the above is optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, or C<sub>1</sub>-C<sub>6</sub> alkoxy.

25     Other even more preferred compound of Z4 include those wherein

- R<sub>110</sub> is furanyl, or benzodioxolyl each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or benzyloxy.
- 30     R<sub>120</sub> is H or benzyl optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, or C<sub>1</sub>-C<sub>6</sub> alkoxy.

Even more preferred compound of Z4 include those wherein

R<sub>110</sub> is furanyl, or benzodioxolyl each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or benzyloxy;

- 5 R<sub>120</sub> is cyclopropyl optionally substituted with C<sub>1</sub>-C<sub>6</sub> alky or phenyl; or cyclopropyl C<sub>1</sub>-C<sub>4</sub> alkyl, wherein each of the above is optionally substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, or C<sub>1</sub>-C<sub>6</sub> alkoxy.

10

Other even more preferred compounds of the instant invention are those wherein

- R<sub>51</sub> at each occurrence is independently H, -SO<sub>2</sub>NH-propyl-OH, -SO<sub>2</sub>NH-ethyl-OH, -SO<sub>2</sub>NH-ethyl-OCH<sub>3</sub>, -SO<sub>2</sub>NH-CH(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>OH, -SO<sub>2</sub>NH-(CH<sub>2</sub>CH(OH)CH<sub>3</sub>), -SO<sub>2</sub>NH-ethyl-NH(CH<sub>3</sub>), -SO<sub>2</sub>NH(CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>, -SO<sub>2</sub>NHCH(CH<sub>3</sub>)CH<sub>2</sub>OH, -SO<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -SO<sub>2</sub>NH(CH<sub>2</sub>CH(OH)CH<sub>3</sub>), -SO<sub>2</sub>-pyrrolidine, -SO<sub>2</sub>-(2,6-dimethylpiperidine), -SO<sub>2</sub>-(2-propylpiperidine), -SO<sub>2</sub>-(hydroxypropyl), -C(O)-(2-methoxymethylpyrrolidine), -C(O)-(2-methylpyrrolidine), -C(O)-(2,6-dimethylpyrrolidine), -C(O)-(2-hydroxymethylpyrrolidine), -C(O)N(methyl)(ethyl), -C(O)N(methyl)(propyl), -C(O)N(methyl)(butyl), -C(O)N(propyl)(butyl), -C(O)N(allyl)(cyclopentyl), -C(O)N(allyl)(cyclohexyl), -C(O)N(methyl)(methyl), -C(O)N(ethyl)(ethyl), -C(O)N(butyl)(butyl), -C(O)N(isopropyl)(isopropyl), -C(O)N(propyl)(propyl), -C(O)N(methyl)(cyclohexyl), -C(O)N(ethyl)(cyclohexyl), -C(O)NH(cyclobutyl), -C(O)NH(cyclopentyl), -C(O)N(CH<sub>3</sub>)(cyclopentyl), -C(O)NH(2-methylcyclohexyl), -C(O)NH(pentyl), -C(O)N(pentyl)(pentyl), -C(O)NH(isopentyl), -C(O)NH(ethoxyethyl), -C(O)N(CH<sub>3</sub>)(methoxyethyl), -C(O)N(propyl)(methoxyethyl), -C(O)N(methoxyethyl)(methoxyethyl), -C(O)N(ethoxyethyl)(ethoxyethyl), -C(O)N(ethyl)(methoxyethyl), -C(O)N(propyl)(hydroxyethyl), -C(O)N(hydroxyethyl)(ethyl),
- 15  
20  
25  
30

ethynyl, methyl, bromo,  $-N(CH_3)SO_2(CH_3)$ ,  $-N(CH_3)SO_2$ -thienyl,  $-N(\text{hydroxypropyl})SO_2CH_3$ ,  $-CH_2-SO_2-(CH_3)$ , or  $-C(O)-CH(CH_3)CH_2CH_2CH_3$ .

Still more preferred are compounds wherein there are two  
 5  $R_{51}$  groups.

Yet even more preferred are compounds wherein the  $R_{51}$  groups are at the 3 and 5 positions of the phenyl group.

More preferred compounds of the instant invention are those wherein

10  $R_{51}$  at each occurrence is independently selected from the group consisting of  $C_1-C_4$  alkyl,  $-C(O)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ ,  $-C(O)NH_2$ ,  $-C(O)N(C_2-C_6 \text{ alkenyl})(C_3-C_8 \text{ cycloalkyl})$ ,  $-C(O)NH(C_3-C_8 \text{ cycloalkyl})$ ,  $-C(O)NH(C_1-C_6 \text{ alkyl})$ ,  $C(O)$ -  
 15 (pyrrolidine) optionally substituted with 1 or two groups that are independently alkoxyalkyl or hydroxy, halogen,  $-C(O)N(C_1-C_6 \text{ hydroxyalkyl})(C_1-C_6 \text{ alkyl})$ ,  $-C(O)NH(\text{alkoxyalkyl})$ ,  $-C(O)N(\text{alkoxyalkyl})(\text{alkoxyalkyl})$ ,  $-C(O)N(C_1-C_6 \text{ alkyl})(\text{alkoxyalkyl})$ ,  $-C(O)N(C_1-C_6 \text{ hydroxyalkyl})(\text{alkyl})$ ,  $-NHSO_2CF_3$ ,  $-N(C_1-C_6 \text{ alkyl})-SO_2$ -thienyl,  $-N(C_1-C_6 \text{ hydroxyalkyl})SO_2-(C_1-C_6$   
 20  $\text{alkyl})$ ,  $-NHC(O)C_1-C_4 \text{ alkyl}$ , oxazolyl optionally substituted with 1 or 2 methyl groups, thiazolyl optionally substituted with 1 or 2 methyl groups, pyrazolyl optionally substituted with 1 or 2 methyl groups, imidazolyl optionally substituted with 1 or 2 methyl groups, isoxazolyl optionally substituted  
 25 with 1 or 2 methyl groups, pyrimidinyl optionally substituted with 1 or 2 methyl or halogen groups,  $-NHSO_2CH_3$ ,  $-NHSO_2$ -imidazolyl wherein the imidazole ring is optionally substituted with 1 or 2 methyl groups,  $-N(C_1-C_6 \text{ alkyl})SO_2(C_1-C_6 \text{ alkyl})$ ,  $-SO_2NH-C_1-C_6 \text{ hydroxyalkyl}$ ,  $-SO_2NH-C_1-C_6 \text{ alkyl}-NH(C_1-C_4 \text{ alkyl})$ ,  
 30  $-SO_2$ -piperazinyl optionally substituted with 1 or 2 methyl groups,  $-SO_2$ -pyrrolidine optionally substituted with 1 or 2 methyl groups,  $-SO_2$ -piperidine optionally substituted with 1 or 2  $C_1-C_4 \text{ alkyl}$  groups,  $-SO_2N(C_1-C_4 \text{ hydroxyalkyl})(C_1-C_4 \text{ hydroxyalkyl})$ ,  $-SO_2NH_2$ ,  $-SO_2N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ ,  $C_2-C_6$



alkynyl,  $-\text{SO}_2-(\text{C}_1-\text{C}_6 \text{ hydroxyalkyl})$ ,  $-\text{SO}_2\text{NH}(\text{C}_1-\text{C}_6 \text{ hydroxyalkyl})$ ,  $-\text{SO}_2\text{N}(\text{C}_1-\text{C}_6 \text{ alkyl})(\text{C}_1-\text{C}_6 \text{ hydroxyalkyl})$ ,  $-(\text{C}_1-\text{C}_4 \text{ alkyl})-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkyl})$ , or  $-\text{C}(\text{O})-(\text{C}_1-\text{C}_{10} \text{ alkyl})$ .

Even more preferred compounds of the instant invention are those wherein  $\text{R}_{51}$  at each occurrence is independently selected from the group consisting of  $-\text{SO}_2\text{NH-propyl-OH}$ ,  $-\text{SO}_2\text{NH-ethyl-OH}$ ,  $-\text{SO}_2\text{NH-ethyl-OCH}_3$ ,  $-\text{SO}_2\text{NH-CH}(\text{CH}_3)_2-\text{CH}_2\text{OH}$ ,  $-\text{SO}_2\text{NH}-(\text{CH}_2\text{CH}(\text{OH})\text{CH}_3)$ ,  $-\text{SO}_2\text{NH-ethyl-NH}(\text{CH}_3)$ ,  $-\text{SO}_2\text{NH}(-\text{CH}_2\text{CH}_2\text{OH})_2$ ,  $-\text{SO}_2\text{NHCH}(\text{CH}_3)\text{CH}_2\text{OH}$ ,  $-\text{SO}_2\text{N}(\text{CH}_3)_2$ ,  $-\text{SO}_2\text{NH}(\text{CH}_2\text{CH}(\text{OH})\text{CH}_3)$ ,  $-\text{SO}_2\text{-pyrrolidine}$ ,  $-\text{SO}_2-(2,6\text{-dimethylpiperidine})$ ,  $-\text{SO}_2-(2\text{-propylpiperidine})$ ,  $-\text{SO}_2-(\text{hydroxypropyl})$ ,  $-\text{C}(\text{O})-(2\text{-methoxymethylpyrrolidine})$ ,  $-\text{C}(\text{O})-(2\text{-methylpyrrolidine})$ ,  $-\text{C}(\text{O})-(2,6\text{-dimethylpyrrolidine})$ ,  $-\text{C}(\text{O})-(2\text{-hydroxymethylpyrrolidine})$ ,  $-\text{C}(\text{O})\text{N}(\text{methyl})(\text{ethyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{methyl})(\text{propyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{methyl})(\text{butyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{propyl})(\text{butyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{allyl})(\text{cyclopentyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{allyl})(\text{cyclohexyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{methyl})(\text{methyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{ethyl})(\text{ethyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{butyl})(\text{butyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{isopropyl})(\text{isopropyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{propyl})(\text{propyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{methyl})(\text{cyclohexyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{ethyl})(\text{cyclohexyl})$ ,  $-\text{C}(\text{O})\text{NH}(\text{cyclobutyl})$ ,  $-\text{C}(\text{O})\text{NH}(\text{cyclopentyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{CH}_3)(\text{cyclopentyl})$ ,  $-\text{C}(\text{O})\text{NH}(2\text{-methylcyclohexyl})$ ,  $-\text{C}(\text{O})\text{NH}(\text{pentyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{pentyl})(\text{pentyl})$ ,  $-\text{C}(\text{O})\text{NH}(\text{isopentyl})$ ,  $-\text{C}(\text{O})\text{NH}(\text{ethoxyethyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{methoxyethyl})(\text{methoxyethyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{CH}_3)(\text{methoxyethyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{propyl})(\text{methoxyethyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{ethoxyethyl})(\text{ethoxyethyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{ethyl})(\text{methoxyethyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{propyl})(\text{hydroxyethyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{hydroxyethyl})(\text{ethyl})$ , ethynyl, methyl, bromo,  $-\text{N}(\text{CH}_3)\text{SO}_2(\text{CH}_3)$ ,  $-\text{N}(\text{CH}_3)\text{SO}_2\text{-thienyl}$ ,  $-\text{N}(\text{hydroxypropyl})\text{SO}_2\text{CH}_3$ ,  $-(\text{CH}_2)-\text{SO}_2-(\text{CH}_3)$ , or  $-\text{C}(\text{O})-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$ .

More preferred compounds of the instant invention are those wherein

$\text{R}_{30}$  is pyridyl which is unsubstituted or substituted with 1 or 2 groups that are independently selected from the group consisting of  $\text{C}_1-\text{C}_4$  alkyl,  $-\text{C}(\text{O})\text{N}(\text{C}_1-\text{C}_6 \text{ alkyl})(\text{C}_1-\text{C}_6 \text{ alkyl})$ ,

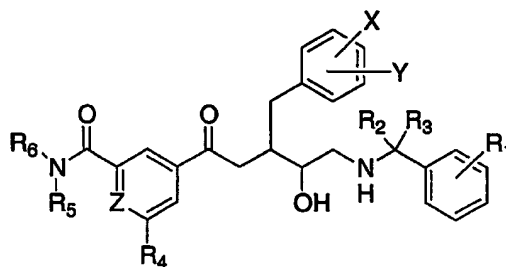
$-C(O)NH_2$ ,  $-C(O)N(C_2-C_6 \text{ alkenyl})(C_3-C_8 \text{ cycloalkyl})$ ,  $-C(O)NH(C_3-C_8 \text{ cycloalkyl})$ ,  $-C(O)NH(C_1-C_6 \text{ alkyl})$ ,  $C(O)-(pyrrolidine)$  optionally substituted with 1 or two groups that are independently alkoxyalkyl or hydroxy, halogen,  $-C(O)N(C_1-C_6$   
 5  $hydroxyalkyl)(C_1-C_6 \text{ alkyl})$ ,  $-C(O)NH(alkoxyalkyl)$ ,  $-C(O)N(alkoxyalkyl)(alkoxyalkyl)$ ,  $-C(O)N(C_1-C_6 \text{ alkyl})(alkoxyalkyl)$ ,  $-C(O)N(C_1-C_6 \text{ hydroxyalkyl})(alkyl)$ ,  $-NHSO_2CF_3$ ,  $-N(C_1-C_6 \text{ alkyl})-SO_2\text{-thienyl}$ ,  $-N(C_1-C_6 \text{ hydroxyalkyl})SO_2-(C_1-C_6 \text{ alkyl})$ ,  $-NHC(O)C_1-C_4 \text{ alkyl}$ , oxazolyl optionally substituted  
 10 with 1 or 2 methyl groups, thiazolyl optionally substituted with 1 or 2 methyl groups, pyrazolyl optionally substituted with 1 or 2 methyl groups, imidazolyl optionally substituted with 1 or 2 methyl groups, isoxazolyl optionally substituted with 1 or 2 methyl groups, pyrimidinyl optionally substituted  
 15 with 1 or 2 methyl or halogen groups,  $-NHSO_2CH_3$ ,  $-NHSO_2\text{-imidazolyl}$  wherein the imidazole ring is optionally substituted with 1 or 2 methyl groups,  $-N(C_1-C_6 \text{ alkyl})SO_2(C_1-C_6 \text{ alkyl})$ ,  $-SO_2NH-C_1-C_6 \text{ hydroxyalkyl}$ ,  $-SO_2NH-C_1-C_6 \text{ alkyl-NH}(C_1-C_4 \text{ alkyl})$ ,  $-SO_2\text{-piperazinyl}$  optionally substituted with 1 or 2 methyl  
 20 groups,  $-SO_2\text{-pyrrolidine}$  optionally substituted with 1 or 2 methyl groups,  $-SO_2\text{-piperidine}$  optionally substituted with 1 or 2  $C_1-C_4 \text{ alkyl}$  groups,  $-SO_2N(C_1-C_4 \text{ hydroxyalkyl})(C_1-C_4 \text{ hydroxyalkyl})$ ,  $-SO_2NH_2$ ,  $-SO_2N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ ,  $C_2-C_6 \text{ alkynyl}$ ,  $-SO_2-(C_1-C_6 \text{ hydroxyalkyl})$ ,  $-SO_2NH(C_1-C_6 \text{ hydroxyalkyl})$ ,  
 25  $-SO_2N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ hydroxyalkyl})$ ,  $-(C_1-C_4 \text{ alkyl})-SO_2-(C_1-C_4 \text{ alkyl})$ , or  $-C(O)-(C_1-C_{10} \text{ alkyl})$ .

Even more preferred compounds of the instant invention are those wherein

30  $R_{30}$  is pyridyl which is unsubstituted or substituted with at least one group that is  $-SO_2NH\text{-propyl-OH}$ ,  $-SO_2NH\text{-ethyl-OH}$ ,  $-SO_2NH\text{-ethyl-OCH}_3$ ,  $-SO_2NH\text{-CH}(\text{CH}_3)_2\text{-CH}_2\text{OH}$ ,  $-SO_2NH\text{-(CH}_2\text{CH}(\text{OH})\text{CH}_3)$ ,  $-SO_2NH\text{-ethyl-NH}(\text{CH}_3)$ ,  $-SO_2NH\text{-(CH}_2\text{CH}_2\text{OH})_2$ ,  $-SO_2NHCH(\text{CH}_3)\text{CH}_2\text{OH}$ ,  $-SO_2N(\text{CH}_3)_2$ ,  $-SO_2NH(\text{CH}_2\text{CH}(\text{OH})\text{CH}_3)$ ,  $-SO_2\text{-pyrrolidine}$ ,  $-SO_2\text{-(2,6-dimethylpiperidine)}$ ,  $-SO_2\text{-(2-propylpiperidine)}$ ,  $-SO_2\text{-}$

- (hydroxypropyl), -C(O)-(2-methoxymethylpyrrolidine), -C(O)-(2-methylpyrrolidine), -C(O)-(2,6-dimethylpyrrolidine), -C(O)-(2-hydroxymethylpyrrolidine), -C(O)N(methyl)(ethyl), -C(O)N(methyl)(propyl), -C(O)N(methyl)(butyl),
- 5 -C(O)N(propyl)(butyl), -C(O)N(allyl)(cyclopentyl), -C(O)N(allyl)(cyclohexyl), -C(O)N(methyl)(methyl), -C(O)N(ethyl)(ethyl), -C(O)N(butyl)(butyl), -C(O)N(isopropyl)(isopropyl), -C(O)N(propyl)(propyl), -C(O)N(methyl)(cyclohexyl), -C(O)N(ethyl)(cyclohexyl),
- 10 -C(O)NH(cyclobutyl), -C(O)NH(cyclopentyl), -C(O)N(CH<sub>3</sub>)(cyclopentyl), -C(O)NH(2-methylcyclohexyl), -C(O)NH(pentyl), -C(O)N(pentyl)(pentyl), -C(O)NH(isopentyl), -C(O)NH(ethoxyethyl), -C(O)N(CH<sub>3</sub>)(methoxyethyl), -C(O)N(propyl)(methoxyethyl),
- 15 -C(O)N(methoxyethyl)(methoxyethyl), -C(O)N(ethoxyethyl)(ethoxyethyl), -C(O)N(ethyl)(methoxyethyl), -C(O)N(propyl)(hydroxyethyl), -C(O)N(hydroxyethyl)(ethyl), ethynyl, methyl, bromo, -N(CH<sub>3</sub>)SO<sub>2</sub>(CH<sub>3</sub>), -N(CH<sub>3</sub>)SO<sub>2</sub>-thienyl, -N(hydroxypropyl)SO<sub>2</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)-SO<sub>2</sub>-(CH<sub>3</sub>), or -C(O)-
- 20 CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>.

Other preferred compounds of the formula X are those of formula Z5



Z5

- 25 or a pharmaceutically acceptable salt thereof, wherein R<sub>1</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, or CF<sub>3</sub>; R<sub>2</sub> and R<sub>3</sub> are both hydrogen; or R<sub>2</sub> and R<sub>3</sub> and the carbon to which they are attached form a cyclopropyl ring;

$R_4$  is oxazolyl optionally substituted with methyl, thiazolyl,  $C_2$ - $C_4$  alkynyl, or  $C_1$ - $C_4$  alkyl;

$R_5$  is  $C_1$ - $C_4$  alkyl;

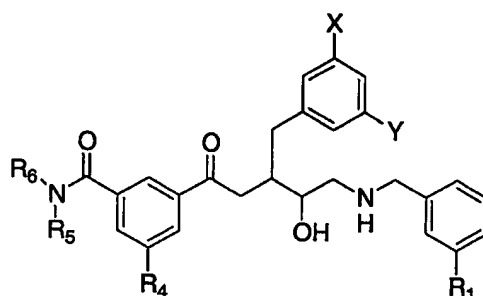
$R_6$  is  $C_1$ - $C_4$  alkyl;

5 X and Y are independently halogen;

Z is CH or N.

Preferred compounds within Formula Z5 are those where Z is CH. Within this group, more preferred are those wherein  $R_2$  and  $R_3$  are both H.

10 Other preferred compounds of the invention are those of formula Z6



Z6

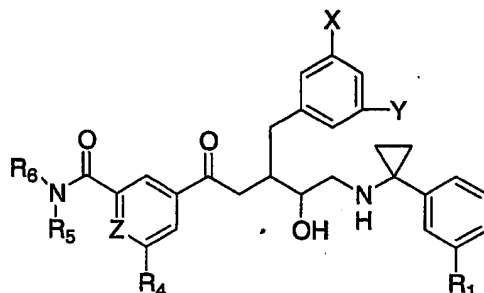
Preferred compounds of Formula Z6 include those where  
 15  $R_1$  is ethyl, ethynyl or  $CF_3$ ; and  $R_4$  is 2-oxazolyl optionally substituted with methyl, 2-thiazolyl, ethynyl, or methyl, hereinafter compounds of Z6-1. Preferred compounds of Z6-1 are those where  $R_5$  is propyl; and  $R_6$  is propyl. More preferably,  $R_1$  is ethyl;  $R_4$  is 2-oxazolyl optionally substituted with methyl;  
 20 and X and Y are both F.

Other preferred compounds of Z6-1 are those where  $R_1$  is ethyl, or  $CF_3$ ; and  $R_4$  is 2-thiazolyl. More preferably,  $R_5$  is propyl; and  $R_6$  is propyl; or  $R_5$  is methyl; and  $R_6$  is propyl or butyl; and X and Y are both F. Still more preferable are  
 25 compounds where  $R_1$  is ethyl. Particularly preferred compounds are those where  $R_1$  is  $CF_3$ ;  $R_5$  is propyl; and  $R_6$  is propyl.

Other preferred compounds of Z6-1 are those where  $R_1$  is ethynyl; and  $R_4$  is ethynyl, methyl, or 2-oxazolyl. More preferably,  $R_5$  is propyl; and  $R_6$  is propyl; and X and Y are

both F. Even more preferred are compounds where  $R_4$  is ethynyl or methyl.

Other preferred compounds of the invention are those of formula Z7

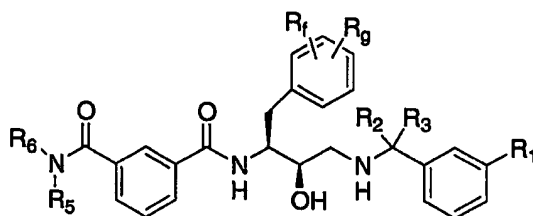


Z7

Preferred compounds of Z7 are those where  $R_1$  is ethyl or ethynyl;  $R_4$  is methyl or 2-oxazolyl, hereinafter compounds of formula Z7-1.

Preferred compounds of Z7-1 include those where  $R_5$  and  $R_6$  are both propyl; and X and Y are both F. More preferably, Z is N; and  $R_4$  is methyl. Even more preferred are compounds of Z7-1 where Z is CH; and  $R_4$  is methyl or 2-oxazolyl.

Other preferred compounds of the invention are those of formula Z8



Z8

or a pharmaceutically acceptable salt thereof, wherein

$R_1$  is  $C_2$ - $C_3$  alkyl;

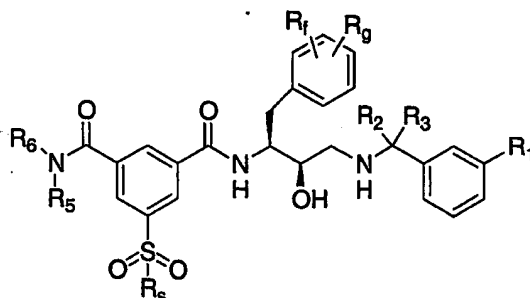
$R_2$  and  $R_3$  are both hydrogen; or

$R_f$  and  $R_g$  are independently halogen;

$R_5$  is  $C_1$ - $C_2$  alkyl sulfonyl;

$R_6$  is hydroxy( $C_1$ - $C_4$ )alkyl, preferably hydroxyethyl or ( $C_1$ - $C_4$ )alkoxy( $C_1$ - $C_4$ )alkyl, preferably methoxyethyl.

Yet other preferred compounds of the invention are those of formula Z9



5

Z9

or a pharmaceutically acceptable salt thereof, wherein

R<sub>1</sub> is C<sub>2</sub>-C<sub>3</sub> alkyl;

R<sub>2</sub> and R<sub>3</sub> are both hydrogen; or

R<sub>f</sub> and R<sub>g</sub> are independently halogen;

10 R<sub>5</sub> and R<sub>6</sub> are independently C<sub>3</sub>-C<sub>4</sub> alkyl; or

R<sub>5</sub> is H and R<sub>6</sub> is C<sub>3</sub> alkyl; or

R<sub>5</sub>, R<sub>6</sub>, and the nitrogen to which they are attached form a pyrrolidinyl ring optionally substituted with methoxymethyl; and

15 R<sub>8</sub> is C<sub>1</sub>-C<sub>2</sub> alkyl, hydroxy(C<sub>2</sub>-C<sub>4</sub>)alkyl, N-[hydroxy(C<sub>2</sub>-C<sub>4</sub>) alkyl]-N-(C<sub>1</sub>-C<sub>2</sub>)alkylamino, N-methyl-N-(C<sub>4</sub> (t-butyl)alkyl)amino, -NH(C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl), -N(C<sub>1</sub>-C<sub>3</sub> hydroxyalkyl)(C<sub>1</sub>-C<sub>3</sub> hydroxyalkyl), -N(C<sub>1</sub>-C<sub>2</sub> alkyl)(C<sub>1</sub>-C<sub>2</sub> alkyl), pyrrolidin-1-yl optionally substituted with hydroxymethyl or  
 20 methoxymethyl, C<sub>1</sub>-C<sub>2</sub> alkoxy C<sub>2</sub>-C<sub>3</sub> alkyl, 1-piperazinyl, -NH<sub>2</sub>, -NH(C<sub>2</sub>-C<sub>3</sub> alkyl-NH(C<sub>1</sub>-C<sub>2</sub> alkyl)), or C<sub>1</sub>-C<sub>4</sub> alkylamino.

Preferred compounds of formula Z9 include those where R<sub>8</sub> is N-[hydroxy(C<sub>4</sub>-alkyl)]-N-methylamino, -N(C<sub>1</sub>-C<sub>3</sub> hydroxyalkyl)(C<sub>1</sub>-C<sub>3</sub> hydroxyalkyl), or -NH(C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl),  
 25 hereinafter compounds of Z9-1.

Preferred compounds of formula Z9-1 include those where the hydroxyalkyl is 2-hydroxy-1,1-dimethylethyl; 2-hydroxyethyl; 3-hydroxypropyl; 1(R)-2-hydroxy-1-methylethyl;

1(S)-2-hydroxy-1-methylethyl; 1(S)-2-hydroxy-1-methylethyl;  
2(R)-2-hydroxypropyl; or 2(S)-2-hydroxypropyl.

Preferred compound of formula Z9 include those wherein  
R<sub>s</sub> is 3-hydroxypropyl, 4-hydroxybutyl.

5 Other preferred compound of formula Z9 include those  
wherein R<sub>s</sub> is 2(R)-2-methoxymethylpyrrolidin-1-yl, 2(R)-2-  
hydroxymethylpyrrolidin-1-yl, 2(S)-2-hydroxymethylpyrrolidin-1-  
yl, pyrrolidin-1-yl or 1-piperazinyl, hereinafter Z9-1A. More  
preferably, R<sub>s</sub> is 2(R)-2-methoxymethylpyrrolidin-1-yl, 2(R)-2-  
10 hydroxymethylpyrrolidin-1-yl, or 2(S)-2-  
hydroxymethylpyrrolidin-1-yl.

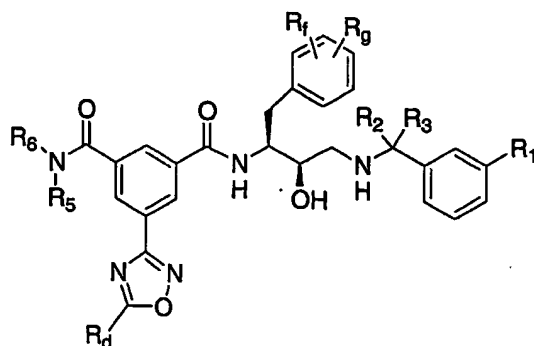
Still other preferred compound of formula Z9 include those  
wherein R<sub>5</sub>, R<sub>6</sub>, and the nitrogen to which they are attached  
form a 2(S)-2-methoxymethylpyrrolidin-1-yl, hereinafter  
15 compounds of Z9-2.

Preferred compound of formula Z9-2 include those wherein  
R<sub>s</sub> is -NH(tert-butyl), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>), -N(CH<sub>3</sub>)<sub>2</sub>, or 2(S)-2-  
methoxymethylpyrrolidin-1-yl, hereinafter Z9-3.

Preferred compounds of formula Z9 include those where R<sub>s</sub>  
20 is N-[hydroxy(C<sub>4</sub> alkyl)]-N-methylamino. Particularly preferred  
are those where R<sub>s</sub> is N-(hydroxy-t-butyl)-N-methylamino. By  
"hydroxy-t-butyl" is meant a 1-Hydroxy-1-methyl-ethyl group.

Other preferred compounds include those of Z9, Z9-1, Z9-  
1A, Z9-2, and Z9-3, wherein R<sub>1</sub> is ethyl or isopropyl. More  
25 preferably, R<sub>1</sub> is ethyl.

Other preferred compounds of the invention are those of  
formula Z10



## Z10

or a pharmaceutically acceptable salt thereof, wherein

$R_1$  is  $C_2$ - $C_3$  alkyl;

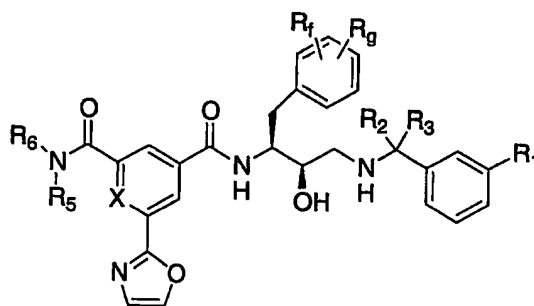
$R_2$  and  $R_3$  are both hydrogen; or

5  $R_f$  and  $R_g$  are independently halogen;

$R_5$  and  $R_6$  are independently  $C_1$ - $C_4$  alkyl; and

$R_d$  is  $C_1$ - $C_2$  alkyl (preferably methyl), N-hydroxy( $C_2$ - $C_3$ )alkyl-N-( $C_1$ - $C_2$ )alkylamino, or  $C_1$ - $C_2$  alkylamino.

Other preferred compounds of the invention are those of  
10 formula Z11



## Z11

or a pharmaceutically acceptable salt thereof, wherein

X is nitrogen or CH;

15  $R_1$  is  $C_2$ - $C_3$  alkyl, amino, mono( $C_1$ - $C_3$ )alkylamino, di( $C_1$ - $C_3$ )alkylamino, amino( $C_1$ - $C_3$ )alkyl, mono( $C_1$ - $C_3$ )alkylamino( $C_1$ - $C_2$ )alkyl, or di( $C_1$ - $C_3$ )alkylamino( $C_1$ - $C_2$ )alkyl;

$R_2$  and  $R_3$  are both hydrogen; or

$R_f$  and  $R_g$  are both hydrogen or independently halogen;

20  $R_5$  and  $R_6$  are independently methyl or  $C_2$ - $C_3$ - $C_4$  alkyl, where at least one of  $R_5$  and  $R_6$  is not methyl.

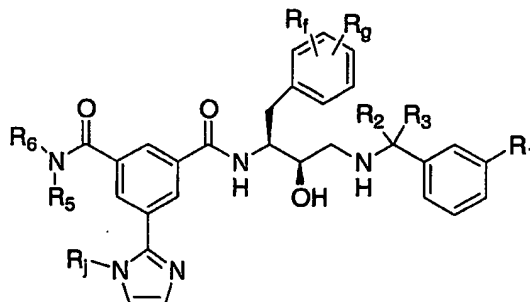
Preferred compounds of Z11 include those where at least one of  $R_5$  and  $R_6$  is  $C_3$  alkyl, hereinafter compounds of Z1-1. Even more preferred compounds of Z11 are those where each of  $R_5$   
25 and  $R_6$  is propyl.

Preferred compounds of Z11 and Z11-1 are those where X is CH. More preferably,  $R_1$  is di( $C_1$ - $C_2$ )alkylamino. Even more preferred are those where at least one of  $R_5$  and  $R_6$  is propyl.



Other preferred compounds of Z11-1 are those where X is nitrogen. More preferably, both of R<sub>5</sub> and R<sub>6</sub> are not methyl. Other more preferred compounds of Z11-1 are those where R<sub>1</sub> is di(C<sub>1</sub>-C<sub>2</sub>)alkylamino(C<sub>1</sub>-C<sub>2</sub>)alkyl. More preferably, the di(C<sub>1</sub>-C<sub>2</sub>)alkylamino(C<sub>1</sub>-C<sub>2</sub>)alkyl group is N,N-dimethyl-(C<sub>1</sub>-C<sub>2</sub>)alkyl.

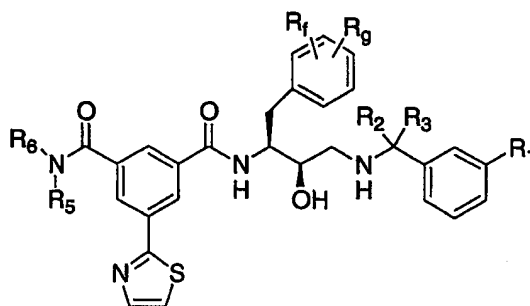
Other preferred compounds of the invention are those of formula Z12



Z12

- or a pharmaceutically acceptable salt thereof, wherein
- R<sub>1</sub> is C<sub>2</sub>-C<sub>3</sub> alkyl,;
- R<sub>2</sub> and R<sub>3</sub> are both hydrogen; or
- R<sub>2</sub>, R<sub>3</sub>, and the carbon to which they are attached form a cyclopropyl ring;
- R<sub>7</sub> and R<sub>8</sub> are independently halogen;
- R<sub>5</sub> and R<sub>6</sub> are independently C<sub>3</sub>-C<sub>4</sub> alkyl (more preferably, at least one of R<sub>5</sub> and R<sub>6</sub> is propyl); and
- R<sub>7</sub> is hydrogen or C<sub>1</sub>-C<sub>2</sub> alkoxymethyl.

Other preferred compounds of the invention are those of formula Z13



Z13

or a pharmaceutically acceptable salt thereof, wherein

$R_1$  is  $C_2$ - $C_4$  alkynyl,  $C_2$ - $C_4$  alkyl preferably ethyl, isopropyl, or trifluoromethyl;

$R_2$  and  $R_3$  are both hydrogen; or

$R_2$  and  $R_3$  together form a 3-membered ring with the carbon atom

5 to which they are attached;

$R_f$  and  $R_g$  are independently halogen; and

$R_5$  and  $R_6$  are independently  $C_3$ - $C_4$  alkyl; or

one of  $R_5$  and  $R_6$  is methyl or ethyl and the other is  $C_3$  or  $C_{4,5}$  (butyl)alkyl.

10

Preferred compounds of formula Z13 include those where  $R_1$  is ethyl, n-propyl, isopropyl, or trifluoromethyl, more preferably ethyl or isopropyl. Even more preferred are compounds where  $R_5$  and  $R_6$  are independently propyl or butyl.

15 Still more preferred are compounds where both of  $R_2$  and  $R_3$  are hydrogen. Particularly preferred are those wherein  $R_f$  and  $R_g$  are both chloro or fluoro.

Other preferred compounds of Z13 are those where  $R_1$  is ethyl or trifluoromethyl, hereinafter compounds of Z13-1.

20 Among these, compounds where  $R_5$  is methyl, ethyl or propyl and  $R_6$  is  $C_3$ - $C_4$  alkyl are more preferred. Even more preferred are those where  $R_6$  is propyl or butyl. Particularly preferred are those where  $R_6$  is butyl and  $R_5$  is methyl.

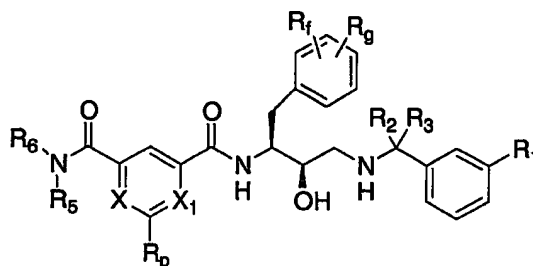
Other preferred compounds of Formula Z13 are those where  
25  $R_5$  is methyl, hereinafter compounds of Z13-2. Preferred compounds of Z13-2 include those where  $R_f$  and  $R_g$  are both chloro or fluoro. More preferably, both of  $R_2$  and  $R_3$  are hydrogen.

Other preferred compounds of Formula Z13 are those wherein  
30 both of  $R_2$  and  $R_3$  are hydrogen; and  
 $R_1$  is  $C_2$ - $C_3$  alkynyl.

Still other preferred compounds of Formula Z13 are those wherein  $R_5$  and  $R_6$  are independently propyl or butyl, hereinafter Z13-3. More preferably, in compounds of Formula

Z13-3, both of  $R_2$  and  $R_3$  are hydrogen. Still more preferably,  $R_f$  and  $R_g$  are both chloro or fluoro. Even more preferably,  $R_2$  and  $R_3$  together form a 3-membered ring with the carbon atom to which they are attached.

- 5 Other preferred compounds of the invention are those of formula Z14



Z14

- or a pharmaceutically acceptable salt thereof, wherein
- 10 one of  $X$  or  $X_1$  is nitrogen or  $N^+-O^-$  while the other is  $CH$ ;  
 $R_1$  is  $C_2$ - $C_4$  alkynyl, cyano, or  $C_1$ - $C_3$  alkyl;  
 $R_2$  and  $R_3$  are both hydrogen; or  
 $R_2$  and  $R_3$  together form a 3-membered ring with the carbon atom  
to which they are attached;
- 15  $R_f$  and  $R_g$  are independently halogen;  
 $R_p$  is hydrogen,  $C_1$ - $C_2$  alkyl, or oxazolyl; and  
 $R_5$  and  $R_6$  are independently  $C_3$ - $C_4$  alkyl.

- Preferred compounds of formula Z14 include those where  $X$   
is nitrogen;  $R_1$  is  $C_1$ - $C_2$  alkyl;  $R_2$  and  $R_3$  are hydrogen; and  $R_p$  is  
20 hydrogen,  $C_1$ - $C_2$  alkyl, or oxazol-2-yl.

- Other preferred compounds of Z14 are those where  $X$  is  
nitrogen;  $R_1$  is  $C_2$ - $C_3$  alkynyl;  $R_2$  and  $R_3$  together form a 3-  
membered ring with the carbon atom to which they are attached;  
and  $R_p$  is  $C_1$ - $C_2$  alkyl. Even more preferred are compounds where  
25  $X$  is nitrogen; and  $R_1$  is  $C_2$  alkynyl.

Other preferred compounds of Z14 are those where  $X$  is  
nitrogen;  $R_1$  is  $C_1$ - $C_2$  alkyl, preferably ethyl;  $R_2$  and  $R_3$  are  
hydrogen; and  $R_p$  is hydrogen,  $C_1$ - $C_2$  alkyl, or oxazol-2-yl.

Still other preferred compounds of Z14 are those where X is nitrogen; R<sub>1</sub> is C<sub>1</sub>-C<sub>2</sub> alkyl; R<sub>2</sub> and R<sub>3</sub> are hydrogen; and R<sub>p</sub> is hydrogen, C<sub>1</sub>-C<sub>2</sub> alkyl, oxazol-2-yl, or cyano. More preferably, R<sub>p</sub> is cyano, methyl or oxazol-2-yl. Even more preferably, R<sub>p</sub> is methyl. Equally preferably, R<sub>p</sub> is oxazol-2-yl. Equally preferably, R<sub>p</sub> is cyano.

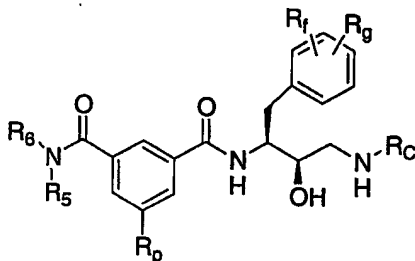
Yet other preferred compounds of Z14 are those wherein X is nitrogen; R<sub>1</sub> is C<sub>2</sub>-C<sub>3</sub> alkyl; R<sub>2</sub> and R<sub>3</sub> together form a 3-membered ring with the carbon atom to which they are attached; and R<sub>p</sub> is C<sub>1</sub>-C<sub>2</sub> alkyl.

Preferred compounds of Z14 include those where R<sub>f</sub> and R<sub>g</sub> are both chloro or fluoro. Still other preferred compounds of Z14 are those where R<sub>5</sub> and R<sub>6</sub> are independently propyl or butyl.

Yet still other compounds of Z14 include those wherein R<sub>f</sub> and R<sub>g</sub> are both chloro or fluoro, and R<sub>5</sub> and R<sub>6</sub> are independently propyl or butyl.

Still other compounds of formula Z14 include those wherein X is CH and X' is N. More preferably, R<sub>p</sub> is cyano, methyl or oxazol-2-yl. More preferably, R<sub>f</sub> and R<sub>g</sub> are both chloro or fluoro, and R<sub>5</sub> and R<sub>6</sub> are independently propyl or butyl. Equally preferably, compounds of Z14 include those wherein R<sub>2</sub> and R<sub>3</sub> together form a 3-membered ring with the carbon atom to which they are attached.

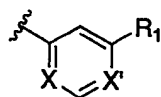
Still other preferred compounds of the invention are those of formula Z15



Z15

or a pharmaceutically acceptable salt thereof, wherein

R<sub>C</sub> is a group of the formula



where one of X and X' is nitrogen and the other is CH and R<sub>1</sub> is C<sub>2</sub>-C<sub>4</sub> alkyl or -(C<sub>1</sub>-C<sub>2</sub> alkyl)-N(C<sub>1</sub>-C<sub>2</sub> alkyl)(C<sub>1</sub>-C<sub>2</sub> alkyl);

5 R<sub>E</sub> and R<sub>G</sub> are independently halogen;

R<sub>P</sub> is C<sub>1</sub>-C<sub>2</sub> alkyl; and

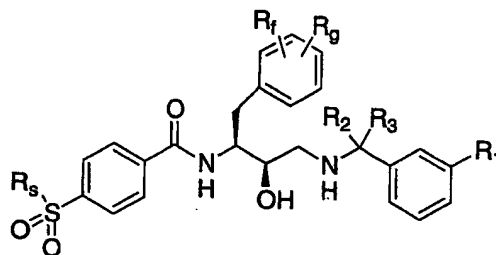
R<sub>5</sub> and R<sub>6</sub> are independently hydrogen or C<sub>3</sub>-C<sub>4</sub> (sec butyl) alkyl.

Preferred compounds of Z15 include those where X is nitrogen; X' is CH; and R<sub>5</sub> and R<sub>6</sub> are independently propyl or  
10 butyl.

Other preferred compounds of Z15 are those where X is CH; X' is nitrogen; and R<sub>5</sub> and R<sub>6</sub> are independently propyl or butyl. More preferably, R<sub>1</sub> is -CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>3</sub>, or ethyl. Still more preferably R<sub>1</sub> is -CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>3</sub>.

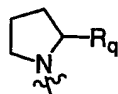
15 Particularly preferred compounds of Z15 include those where one of R<sub>5</sub> and R<sub>6</sub> is hydrogen and the other is C<sub>4</sub> butyl, more preferably sec-butyl.

Other preferred compounds of the invention are those of formula Z16



Z16

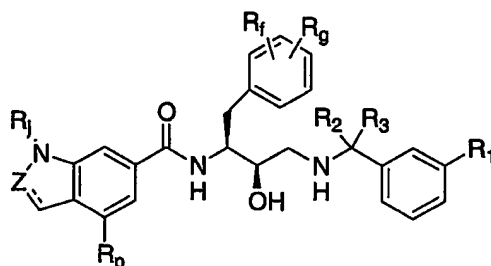
or a pharmaceutically acceptable salt thereof, wherein R<sub>8</sub> is methylamino, ethylamino, C<sub>3</sub> alkylamino, di(C<sub>3</sub>-alkyl)amino, or a group of the formula



25 where R<sub>q</sub> is C<sub>1</sub>-C<sub>2</sub> alkoxy(C<sub>1</sub>-C<sub>2</sub>)alkyl;  
R<sub>1</sub> is C<sub>2</sub>-C<sub>3</sub> alkyl;

$R_2$  and  $R_3$  are both hydrogen; and  
 $R_f$  and  $R_g$  are independently halogen.

Other preferred compounds of the invention are those of  
 formula Z17



Z17

- or a pharmaceutically acceptable salt thereof, wherein  
 Z is  $\text{CH}_2$  when the dashed line represents a single bond or CH or  
 a nitrogen atom when the dashed line represents a double  
 bond;  
 $R_1$  is  $\text{C}_2\text{-C}_3$  alkyl;  
 $R_2$  and  $R_3$  are both hydrogen; or  
 $R_2$ ,  $R_3$  and the carbon to which they are attached form a  
 cyclopropyl ring;  
 $R_f$  and  $R_g$  are independently halogen;  
 $R_p$  is hydrogen, cyano,  $\text{C}_1\text{-C}_3$  alkyl, amino,  $\text{N-(C}_1\text{-C}_3$   
 alkylsulfonyl)- $\text{N-((C}_1\text{-C}_3\text{)alkyl)amino}$  (good when  $\text{Z=CH}$ ), 2-  
 oxazolyl, or 1-pyrrolyl optionally substituted in the 2  
 and 5 positions with  $\text{C}_1\text{-C}_2$  alkyl; and  
 $R_j$  is  $\text{C}_1\text{-C}_5$  alkyl.

Preferred compounds of formula Z17 include those where  $R_p$   
 is  $\text{-N(CH}_3\text{)SO}_2(\text{C}_1\text{-C}_2 \text{ alkyl})$ ; and  $R_1$  is ethyl.

Other preferred compounds of formula Z17 include those  
 where Z is  $\text{CH}_2$ , hereinafter compounds of Z17-1. Preferred  
 compounds of Z17-1 include those where  $R_p$  is  $\text{N-(C}_1\text{-C}_3$   
 alkylsulfonyl)- $\text{N-((C}_1\text{-C}_3\text{)alkyl)amino}$ .

Other preferred compounds of Z17 are those where  $R_j$  is  
 methyl.

Still other preferred compounds of Z17-1 are those where  $R_p$  is N-(methylsulfonyl)-N-((C<sub>1</sub>-C<sub>2</sub>)alkyl)amino; and  $R_j$  is C<sub>3</sub>-C<sub>4</sub> alkyl, preferably butyl, hereinafter Z17-2.

Preferred compounds of Z17-2 include those wherein  $R_p$  is  
 5 -N(CH<sub>3</sub>)SO<sub>2</sub>(C<sub>1</sub>-C<sub>2</sub> alkyl); and  $R_1$  is ethyl.

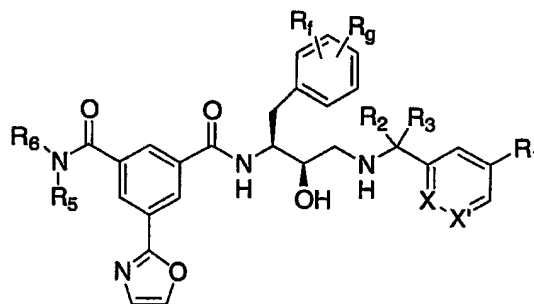
Other preferred compounds of Z17 are those where  $R_p$  is 2-oxazolyl. In these compounds, Z is preferably CH<sub>2</sub> or CH. More preferably, Z is CH.

Other preferred compounds of Z17 are those where  $R_p$  is  
 10 cyano; Z is CH<sub>2</sub> or CH; and  $R_j$  is C<sub>3</sub>-C<sub>4</sub> alkyl. Preferably, Z is CH and  $R_j$  is butyl.

Still other preferred compounds of Z17, Z17-1, and Z17-2 are those wherein at least one of  $R_f$  and  $R_g$  is fluorine. More preferably, both are fluorine.

15 Still other preferred compounds of Z17, Z17-1, and Z17-2 are those wherein  $R_2$ ,  $R_3$ , and the carbon to which they are attached form a cyclopropyl ring.

Other preferred compounds of the invention are those of formula Z18



Z18

or a pharmaceutically acceptable salt thereof, wherein both of X and X' are CH, or one of X and X' is nitrogen and the other is CH;

25  $R_1$  is C<sub>2</sub>-C<sub>3</sub> alkynyl, C<sub>1,2</sub>-C<sub>3</sub> alkyl, amino, mono(C<sub>1</sub>-C<sub>3</sub>)alkylamino, or di(C<sub>1</sub>-C<sub>3</sub>) alkylamino, aminoalkyl, mono(C<sub>1</sub>-C<sub>3</sub>)alkylamino(C<sub>1</sub>-C<sub>2</sub>)alkyl, di(C<sub>1</sub>-C<sub>3</sub>)alkylamino(C<sub>1</sub>-C<sub>2</sub>)alkyl, CF<sub>3</sub>, C<sub>1</sub>-C<sub>2</sub> alkoxy, halogen, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>2</sub> alkyl);

R<sub>2</sub> and R<sub>3</sub> are both hydrogen; or

R<sub>2</sub> and R<sub>3</sub> together form a 3-membered ring with the carbon atom to which they are attached;

R<sub>f</sub> and R<sub>g</sub> are both hydrogen or independently halogen;

5 R<sub>5</sub> and R<sub>6</sub> are independently C<sub>1,2,3</sub>-C<sub>4</sub> alkyl; or

one of R<sub>5</sub> and R<sub>6</sub> is methyl or ethyl and the other is C<sub>3</sub> or C<sub>4</sub> alkyl, preferably butyl.

Preferred compounds of Formula Z18 include those where R<sub>1</sub>  
10 is bromo or chloro.

Other preferred compounds of Z18 include those of Z18-1, i.e., compounds of formula Z18 where R<sub>1</sub> is C<sub>2</sub>-C<sub>3</sub> alkyl.

Other preferred compounds of Z18 include those of Z18-2, i.e., compounds of formula Z18 where R<sub>1</sub> is di(C<sub>1</sub>-C<sub>3</sub>)alkylamino  
15 and both of R<sub>f</sub> and R<sub>g</sub> are chloro or fluoro.

Still other preferred compounds of Z18 include those of Z18-3, i.e., compounds of formula Z18 where R<sub>1</sub> is di(C<sub>1</sub>-C<sub>3</sub>)alkylamino(C<sub>1</sub>-C<sub>2</sub>)alkyl, and both of R<sub>f</sub> and R<sub>g</sub> are chloro or fluoro.

20 More preferred compounds of formula Z18 include those where X is nitrogen; R<sub>f</sub> and R<sub>g</sub> are both fluoro; R<sub>1</sub> is C<sub>1</sub>-C<sub>3</sub> alkyl; and R<sub>2</sub> and R<sub>3</sub> together form a 3-membered ring with the carbon atom to which they are attached.

Preferred compounds of Z18-1 include those where both X  
25 and X' are CH; and R<sub>f</sub> and R<sub>g</sub> are both chloro or fluoro, hereinafter compounds of formula Z18-1-A. More preferred compounds of Z18-1 and Z18-1-A are those where one of R<sub>5</sub> and R<sub>6</sub> is methyl or ethyl and the other is C<sub>3</sub> or C<sub>4</sub> alkyl, preferably butyl.

30 Still other more preferred compounds of Z18-1 include compounds of formula Z18-1-B, i.e., compounds of Z18-1 where R<sub>5</sub> and R<sub>6</sub> are independently C<sub>2</sub>-C<sub>4</sub> alkyl. Preferred compounds of Z18-1-B include those where R<sub>5</sub> is C<sub>2</sub>-C<sub>4</sub> alkyl and R<sub>6</sub> is ethyl.



Other preferred compounds of Z18-1-A are those where one of  $R_5$  and  $R_6$  is methyl or ethyl and the other is  $C_3$  or  $C_4$  alkyl, preferably butyl. More preferably, one of  $R_5$  and  $R_6$  is methyl. Yet other preferred compounds of Z18-1-A are those  
 5 where  $R_5$  and  $R_6$  are independently propyl or butyl.

Other preferred compounds of formula Z18 are compounds of formula Z18-4, i.e., compounds of formula Z18 where  $R_1$  is  $C_2$  alkynyl. Preferred compounds of Z18-4 include those where both  
 10 X and X' are CH; and  $R_f$  and  $R_g$  are both chloro or fluoro.

Other preferred compounds of Z18-4 include those wherein X is nitrogen and X' is  $CH_3$ .

Other preferred compounds of Z18-1-A are those where  $R_5$  and  $R_6$  are independently propyl or butyl.

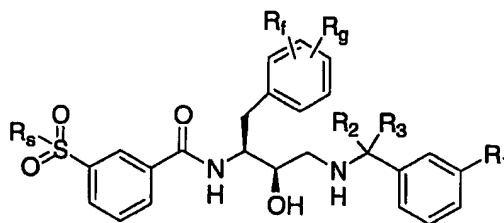
15 Still other preferred compounds of Z18 include those compounds wherein  $R_1$  is  $CF_3$ , or  $-NHSO_2CH_3$ ;  $R_2$  and  $R_3$  are both H; and  $R_5$  and  $R_6$  are independently  $C_3$  or  $C_4$  alkyl, hereinafter Z18-5.

Yet still other preferred compounds of Z18 include those  
 20 wherein X is CH and X' is nitrogen, hereinafter Z18-6.

Preferred compounds of any of the embodiments of Z18, Z18-1-A, -1-B, Z18-2, Z18-3, Z18-4, Z18-5, Z18-6 are those where  $R_2$  and  $R_3$  together form a 3-membered ring with the carbon atom to which they are attached, hereinafter Z18-7.

25 More preferred compounds of Z18-7 include those wherein at least one of  $R_f$  and  $R_g$  is fluoro. More preferably, both  $R_f$  and  $R_g$  are fluoro.

Other preferred compounds of the invention are those of formula Z19



## Z19

or a pharmaceutically acceptable salt thereof, wherein

R<sub>1</sub> is C<sub>2</sub>-C<sub>3</sub> alkyl, or C<sub>1</sub>-C<sub>2</sub> alkoxy;

R<sub>2</sub> and R<sub>3</sub> are both hydrogen;

5 R<sub>f</sub> and R<sub>g</sub> are independently halogen;

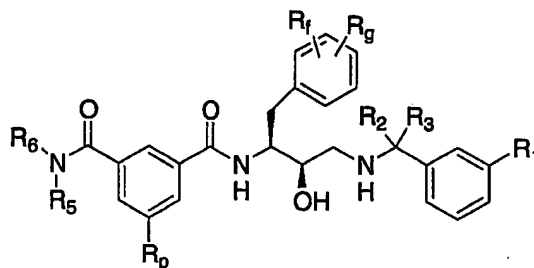
R<sub>s</sub> is C<sub>3</sub>-C<sub>9</sub> alkyl (preferably C<sub>3</sub>-C<sub>4</sub> alkyl), thiazolinyl or thiazolidinyl.

Preferred compounds of formula Z19 include those where R<sub>s</sub> is 2-thiazolidinyl or 2-thiazolinyl and R<sub>1</sub> is C<sub>2</sub>-C<sub>3</sub> alkyl.

10 Other preferred compounds of Z19 are those where R<sub>s</sub> is methyl, propyl or, more preferably, t-butyl. Still more preferably at least one of R<sub>f</sub> and R<sub>g</sub> is fluoro. Even more preferably, R<sub>1</sub> is also C<sub>2</sub>-C<sub>3</sub> alkyl.

Other preferred compounds of formula Z19 include those  
15 wherein R<sub>s</sub> is C<sub>8</sub> alkyl. More preferably, the C<sub>8</sub> alkyl is -CH<sub>2</sub>CH(n-propyl)(n-propyl). Even more preferably R<sub>1</sub> is also C<sub>1</sub>-C<sub>2</sub> alkoxy. Even more preferably, R<sub>1</sub> is methoxy.

Other preferred compounds of the invention are those of formula Z20



20

## Z20

or a pharmaceutically acceptable salt thereof, wherein

R<sub>1</sub> is C<sub>2</sub>-C<sub>3</sub> alkyl, CF<sub>3</sub>, or -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl);

R<sub>2</sub> and R<sub>3</sub> are both hydrogen; or

25 R<sub>2</sub> and R<sub>3</sub> together with the carbon atom to which they are attached form a 3-membered ring;

R<sub>p</sub> is pyridyl, piperazinyl, amino, amino(C<sub>1</sub>-C<sub>5(3)</sub>)alkyl, mono(C<sub>1</sub>-C<sub>2</sub>)alkylamino(C<sub>1</sub>-C<sub>5</sub>)alkyl, di(C<sub>1</sub>-C<sub>2</sub>)alkylamino(C<sub>1</sub>-C<sub>(4)5</sub>)alkyl, mono(C<sub>1</sub>-C<sub>3</sub>)alkylamino, di(C<sub>1</sub>-C<sub>3</sub>)alkylamino,

amino(C<sub>3</sub>-C<sub>4</sub>)alkynyl, mono(C<sub>1</sub>-C<sub>2</sub>)alkylamino(C<sub>3</sub>-C<sub>4</sub>)alkynyl,  
di(C<sub>1</sub>-C<sub>2</sub>)alkylamino(C<sub>3</sub>-C<sub>5</sub>)alkynyl, -N(C<sub>1</sub>-C<sub>2</sub> alkyl)-SO<sub>2</sub>(C<sub>1</sub>-C<sub>2</sub>  
alkyl), -NH-SO<sub>2</sub>(C<sub>1</sub>-C<sub>2</sub> alkyl), -N(C<sub>1</sub>-C<sub>2</sub> alkyl)-SO<sub>2</sub>-thienyl,  
-N(C<sub>1</sub>-C<sub>2</sub> alkyl)-SO<sub>2</sub>(C<sub>1</sub>-C<sub>2</sub> haloalkyl), di(C<sub>1</sub>-  
5 C<sub>2</sub>)alkylamino(C<sub>3</sub>-C<sub>4</sub>)alkynyl, pyrimidinyl, pyrazolyl,  
imidazolyl, or C<sub>2</sub>-C<sub>4</sub> alkynyl;

R<sub>f</sub> and R<sub>g</sub> are independently halogen;

R<sub>5</sub> and R<sub>6</sub> are independently C<sub>3</sub>-C<sub>4</sub> alkyl.

Preferred compounds of Formula Z20 include those of  
10 formula Z20-1, i.e., compounds of Z20 where R<sub>5</sub> and R<sub>6</sub> are both  
C<sub>3</sub> alkyl.

Other preferred compounds of Formula Z20 include those of  
formula Z20-2, i.e., compounds of Z20 where R<sub>2</sub> and R<sub>3</sub> are  
hydrogen.

15 Still other preferred compounds of Z20 are compounds of  
formula Z20-3, i.e., compounds of Z20 where R<sub>2</sub> and R<sub>3</sub> together  
form a 3-membered ring with the carbon atom to which they are  
attached.

Preferred compounds of Z20-1, -2, and -3 are those where  
20 R<sub>p</sub> is 4-pyridyl, 2-pyrimidinyl, 4-pyrazolyl, or 4-imidazolyl,  
more preferably R<sub>p</sub> is 4-pyridyl, hereinafter Z20-3A. Other  
preferred compounds of formulas Z20-1, -2, and -3 are those  
where R<sub>p</sub> is diethylamino or dimethylamino, hereinafter Z20-3B.  
Still other preferred compounds of formulas Z20-1, -2, and -3  
25 are those R<sub>p</sub> is amino or C<sub>1</sub>-C<sub>6</sub> alkylamino, hereinafter Z20-3C.  
Yet other preferred compounds of Z20-1, -2, and -3 are those  
where R<sub>p</sub> is 1-piperazinyl, hereinafter Z20-3D. Still other  
preferred compounds of Z20-1, -2, and -3 include compounds  
where R<sub>p</sub> is amino(C<sub>2</sub>-C<sub>4</sub>)alkyl where the amino is optionally mono  
30 substituted with C<sub>1</sub>-C<sub>2</sub> alkyl, hereinafter Z20-3E; or where R<sub>p</sub> is  
-N(CH<sub>3</sub>)-SO<sub>2</sub>CH<sub>3</sub>, -NH-SO<sub>2</sub>CH<sub>3</sub>, -N(CH<sub>3</sub>)-SO<sub>2</sub>-thien-2-yl, or -N(CH<sub>3</sub>)-  
SO<sub>2</sub>CF<sub>3</sub>, hereinafter Z20-3F.

Other preferred compounds of Z20 are those where  $R_p$  is di( $C_1$ - $C_2$ )alkylamino( $C_3$ - $C_5$ )alkyl, more preferably, N,N-dimethylamino( $C_3$ - $C_5$ )alkyl, hereinafter Z20-3G.

Particularly preferred compounds of Z20-1, -2, and -3 are those where  $R_p$  is 3-(mono( $C_1$ - $C_2$ )alkylamino)propyn-1-yl, hereinafter Z20-3H. Other particularly preferred compounds of Z20 are those where  $R_p$  is 3-(mono( $C_1$ - $C_2$ )alkylamino)propyn-1-yl, 3-(di( $C_1$ - $C_2$ )alkylamino)propyn-1-yl, or 4-(di( $C_1$ - $C_2$ )alkylamino)propyn-1-yl, hereinafter Z20-3I.

Other preferred compounds of Z20, Z20-1, -2, and -3 are those where  $R_p$  is di( $C_1$ - $C_2$ )alkylamino( $C_3$ - $C_5$ )alkyl; and  $R_5$  and  $R_6$  are both  $C_3$  alkyl, hereinafter Z20-3J.

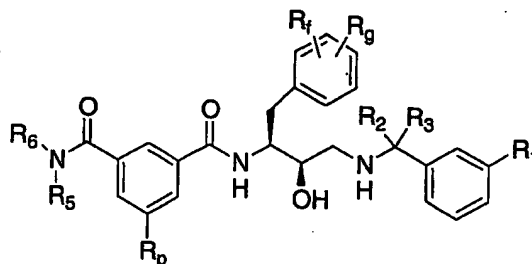
Still other preferred compounds of Z20, Z20-1, -2, -3, are those where  $R_p$  is  $C_2$ - $C_3$  alkynyl, hereinafter Z20-4. More preferably,  $R_p$  is  $C_2$  alkynyl.

Also preferred are compounds of formulas Z20, Z20-1, -2, -3, -3A to -3J and Z20-4 when  $R_1$  is  $-NH(C_3$ - $C_6$  cycloalkyl) preferably  $-NH$ cyclopropyl. More preferably, at least one of  $R_f$  and  $R_g$  is fluoro. Even more preferably, both are fluoro.

Also preferred are compounds of formulas Z20, Z20-1, -2, -3, -3A to -3J and Z20-4 when  $R_1$  is  $CF_3$ . More preferably, at least one of  $R_f$  and  $R_g$  is fluoro. Even more preferably, both are fluoro.

Other preferred compounds of Z20, Z20-1, -2, -3, -3A to -3J and -4 include those wherein  $R_1$  is ethyl or isopropyl. Preferably  $R_1$  is isopropyl. More preferably  $R_1$  is ethyl. More preferably, at least one of  $R_f$  and  $R_g$  is fluoro. Even more preferably, both are fluoro. Still more preferably,  $R_f$  and  $R_g$  are attached to the 3 and 5 positions of the phenyl ring (with position 1 being the point of attachment to the  $CH_2$  group.)

Other preferred compounds of the invention are those of formula Z21.



Z21

or a pharmaceutically acceptable salt thereof, wherein

R<sub>1</sub> is C<sub>2</sub>-C<sub>3</sub> alkynyl;

5 R<sub>2</sub> and R<sub>3</sub> are both hydrogen;

R<sub>p</sub> is C<sub>1</sub>-C<sub>3</sub> alkyl;

R<sub>f</sub> and R<sub>g</sub> are independently halogen;

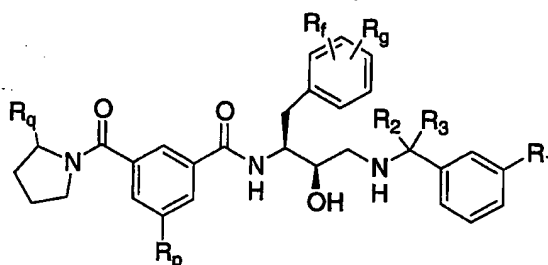
R<sub>5</sub> and R<sub>6</sub> are independently C<sub>3</sub>-C<sub>4</sub> alkyl; or

one of R<sub>5</sub> and R<sub>6</sub> is methyl and the other is C<sub>3</sub> or C<sub>4</sub> alkyl.

10 Preferred compounds of formula Z21 include those where one of R<sub>5</sub> and R<sub>6</sub> is methyl and the other is butyl, herein after Z21-1.

Other preferred compounds of formula Z21 and Z21-1 include those where R<sub>p</sub> is methyl.

15 Other preferred compounds of the invention are those of formula Z22



Z22

20 or a pharmaceutically acceptable salt thereof, wherein

R<sub>1</sub> is C<sub>1</sub>-C<sub>2</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkynyl or C<sub>3</sub> (isopropyl)-C<sub>4</sub> alkyl;

R<sub>2</sub> and R<sub>3</sub> are both hydrogen; or

R<sub>2</sub> and R<sub>3</sub> together form a 3-membered ring with the carbon atom to which they are attached;

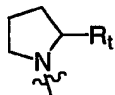
25 R<sub>f</sub> and R<sub>g</sub> are independently halogen;

$R_p$  is  $C_1$ - $C_3$  alkyl or a group of the formula:

$R_sSO_2$ - where  $R_s$  is

$R_{51}R_{61}N$ - and  $R_{51}$  and  $R_{61}$  independently represent  
hydrogen or  $C_1$ - $C_4$  alkyl groups; or

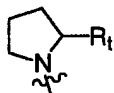
5 a group of the formula:



where  $R_t$  is  $C_1$ - $C_2$  alkoxy( $C_1$ - $C_2$ )alkyl; and

$R_q$  is  $C_1$ - $C_3$  alkoxy( $C_1$ - $C_2$ )alkyl,  $C_1$ - $C_4$  alkyl,  $-C(O)NH_2$ , or H.

Preferred compounds of formula Z22 include those where  $R_1$   
is  $C_2$  alkynyl;  $R_2$  and  $R_3$  together form a 3-membered ring with  
10 the carbon atom to which they are attached; and  $R_p$  is  $R_sSO_2$ -



where  $R_s$  is .

Other preferred compounds of formula Z22 include those  
where  $R_1$  is  $C_1$ - $C_2$  alkyl;  $R_2$  and  $R_3$  are hydrogen; and  $R_p$  is  $R_sSO_2$ -  
where  $R_s$  is  $C_3$ - $C_4$  amino, preferably propyl, more preferably t-  
15 butylamino.

Still other preferred compounds of formula Z22 include  
those where  $R_1$  is  $C_1$ - $C_2$  alkyl;  $R_2$  and  $R_3$  are hydrogen;  $R_p$  is  $C_1$ - $C_2$   
alkyl; and  $R_q$  is  $C_3$ - $C_4$  alkyl, preferably propyl or butyl.

Yet other preferred compounds of formula Z22 include those  
20 where  $R_1$  is  $C_1$ - $C_2$  alkyl;  $R_2$  and  $R_3$  are hydrogen;  $R_p$  is  $C_1$ - $C_2$   
alkyl; and  $R_q$  is propoxy( $C_1$ - $C_2$ )alkyl.

Other preferred compounds of formula Z22 include those  
where  $R_1$  is  $C_1$ - $C_2$  alkyl;  $R_2$  and  $R_3$  are hydrogen;  $R_p$  is  $C_1$ - $C_2$   
alkyl; and  $R_q$  is methoxy( $C_1$ - $C_2$ )alkyl.

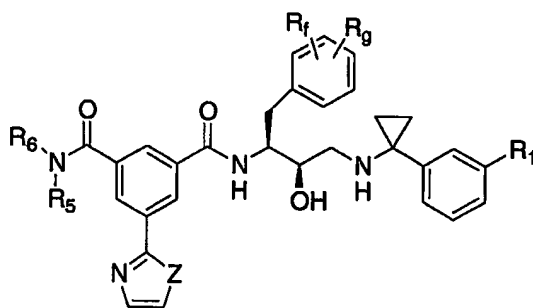
25 Other preferred compounds of formula Z22 include those  
where  $R_1$  is  $C_1$ - $C_2$  alkyl;  $R_2$  and  $R_3$  together form a 3-membered  
ring with the carbon atom to which they are attached;  $R_p$  is  $C_1$ -  
 $C_2$  alkyl; and  $R_q$  is  $C_1$ - $C_2$  alkyl.

Other preferred compounds of formula Z22 include those  
30 where  $R_1$  is  $C_1$ - $C_2$  alkyl;  $R_2$  and  $R_3$  are hydrogen;  $R_p$  is  $C_1$ - $C_2$   
alkyl; and  $R_q$  is  $C_1$ - $C_2$  alkyl.

Particularly preferred are compounds of Z22 where R<sub>1</sub> is isopropyl.

Other preferred compounds of Z22 include those wherein R<sub>4</sub> is (R)-methoxymethyl, methyl, propyl, (S)-propyl, (R)-propyl, butyl, (R)-butyl, (S)-butyl, (R)-2-methoxymethyl, or (R)-2-methoxyethyl.

Other preferred compounds of the invention are those of formula Z23



Z23

or a pharmaceutically acceptable salt thereof, wherein Z is oxygen, nitrogen, or sulfur;

R<sub>1</sub> is chloro, bromo, hydrogen or C<sub>1</sub>-C<sub>2</sub> alkyl;

R<sub>f</sub> and R<sub>g</sub> are independently halogen; and

R<sub>5</sub> and R<sub>6</sub> are independently C<sub>3</sub>-C<sub>4</sub> alkyl; or

one of R<sub>5</sub> and R<sub>6</sub> is methyl and the other is C<sub>3</sub> or C<sub>4</sub> alkyl.

Preferred compounds of Formula Z23 include those where Z is nitrogen; and R<sub>1</sub> is C<sub>1</sub>-C<sub>3</sub> alkyl.

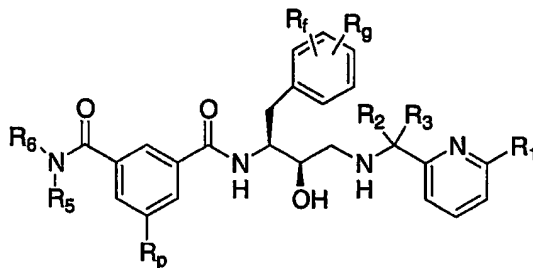
Preferred compounds of formula Z23 are those where R<sub>1</sub> is bromo, and Z is oxygen, hereinafter Z23-1. Other preferred compounds of formula Z23 are those wherein Z is nitrogen, hereinafter Z23-2. Still other preferred compounds of formula Z23 are those wherein Z is sulfur, hereinafter compounds of formula Z23-3.

Particularly preferred compounds of Z23, Z23-1, Z23-2, and Z23-3 are those where one of R<sub>5</sub> and R<sub>6</sub> is methyl and the other is butyl. Equally preferred are those where at least one of R<sub>5</sub>

and  $R_6$  is propyl. Still more preferably,  $R_1$  is  $C_1$ - $C_3$  alkyl. Even more preferably,  $R_1$  is  $C_2$ - $C_3$  alkyl.  $R_1$  can also be ethyl.

Other preferred compounds of the invention are those of formula Z24

5



Z24

or a pharmaceutically acceptable salt thereof, wherein

$R_1$  is  $C_1$ - $C_2$ - $C_3$  alkyl,;

10  $R_2$  and  $R_3$  are both hydrogen; or

$R_p$  is  $C_1$ - $C_2$  alkyl;

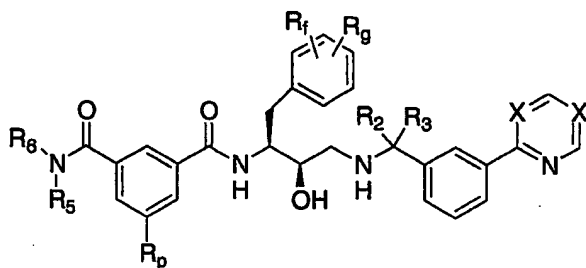
$R_f$  and  $R_g$  are both hydrogen or independently halogen; and

$R_5$  and  $R_6$  are independently  $C_3$ - $C_4$  alkyl.

Preferred compounds of formula Z24 include those where  $R_1$   
 15 is ethyl. More preferably,  $R_p$  is also methyl. Still more preferably,  $R_f$  and  $R_g$  are both halogen.

Other preferred compounds of the invention are those of formula Z25

20



Z25

or a pharmaceutically acceptable salt thereof, wherein

one of X and X' is nitrogen and the other is CH or  $CR_1$ ;

$R_1$  is  $C_1$ - $C_2$ - $C_3$  alkyl

25  $R_2$  and  $R_3$  are both hydrogen; or



$R_2$ ,  $R_3$ , and the carbon to which they are attached form a cyclopropyl ring;

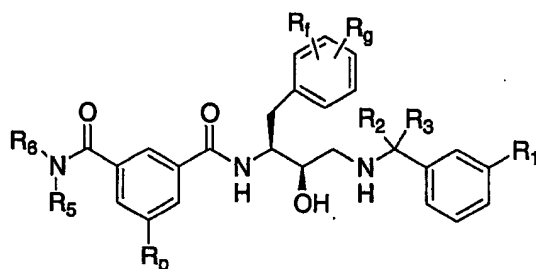
$R_p$  is  $C_1$ - $C_2$  alkyl;

$R_f$  and  $R_g$  are independently halogen; and

5  $R_5$  and  $R_6$  are independently  $C_3$ - $C_4$  alkyl.

Preferred compounds of Z25 include compounds where X is CH and X' is nitrogen. Particularly preferred compounds of formula Z25 include those where  $R_1$  is ethyl. Even more preferred is when  $R_2$  and  $R_3$  are both hydrogen.

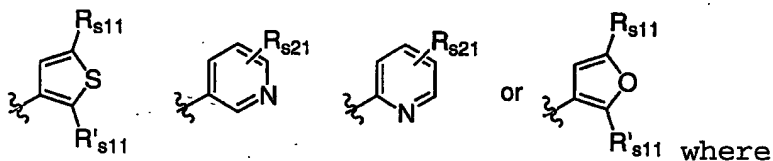
10 Other preferred compounds of the invention are those of formula Z26



Z26

or a pharmaceutically acceptable salt thereof, wherein

15  $R_1$  is a group of the formula:



one of  $R_{s11}$  and  $R'_{s11}$  is hydrogen and the other is  $C_1$ - $C_3$  acyl,  $C_1$ - $C_2$  alkyl or CHO; or

one of  $R_{s11}$  and  $R'_{s11}$  is methyl and the other is CHO or methyl,

each  $R_{s21}$  is  $C_1$ - $C_3$  alkoxy, halogen, H,  $C_1$ - $C_2$  alkyl or cyano; or

$R_1$  is cyclopentyl, cyclohexyl, oxazolyl, isoxazolyl optionally substituted with one or two  $C_1$ - $C_2$  alkyl groups, phenyl, thien-2-yl optionally substituted with CHO, unsubstituted thien-3-yl;

$R_2$  and  $R_3$  are both hydrogen;

$R_p$  is  $C_1$ - $C_2$  alkyl;

$R_f$  and  $R_g$  are independently halogen; and

$R_5$  and  $R_6$  are independently  $C_3$ - $C_4$  alkyl.

Preferred compounds of formula Z26 include compounds of  
 5 Z26 where  $R_1$  is 6-( $C_1$ - $C_2$ )alkoxypyridin-2-yl.

Other preferred compounds of formula Z26 include compounds  
 of Z26 where  $R_1$  is 2-formylthien-3-yl.

Still other preferred compounds of formula Z26 include  
 compounds of Z26 where  $R_1$  is 5-formylthien-3-yl.

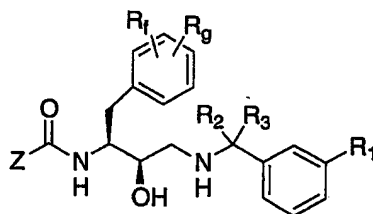
10 Other preferred compounds of formula Z26 include compounds  
 where  $R_{s21}$  is cyano.

Yet other preferred compounds of formula Z26 include  
 compounds of Z26 where  $R_1$  is 5-cyanopyrid-3-yl.

Other preferred compounds of formula Z26 are those of  
 15 formula Z26-1, i.e., compounds of Z26 where  $R_1$  is 6-halopyrid-  
 3-yl. Particularly preferred compounds of Z26-1 are those  
 where halogen in  $R_1$  is fluoro or chloro.

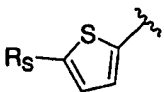
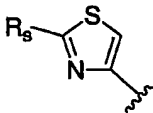
Still other preferred compounds of formula Z26 are those  
 wherein  $R_1$  is a thienyl group optionally substituted with  $R_{s11}$ ,  
 20 or  $R'_{s11}$ , cyclopentyl, cyclohexyl, oxazolyl, isoxazolyl  
 optionally substituted with one or two  $C_1$ - $C_2$  alkyl groups,  
 phenyl, or thien-2-yl optionally substituted with CHO. More  
 preferably, the unsubstituted thienyl group is a thien-3-yl or  
 a thien-2-yl.

25 Other preferred compounds of the invention are those of  
 formula Z27



Z27

or a pharmaceutically acceptable salt thereof, wherein

Z is , , pyridyl or the pyridyl N-oxide wherein the pyridyl or the pyridyl N-oxide is substituted with C(O)NR<sub>5</sub>R<sub>6</sub>, wherein

R<sub>5</sub> and R<sub>6</sub> are independently C<sub>3</sub>-C<sub>4</sub> alkyl; or

5 R<sub>5</sub> is methyl or ethyl and R<sub>6</sub> is C<sub>3</sub> alkyl;

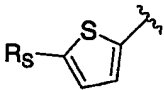
R<sub>1</sub> is C<sub>1</sub>-C<sub>3</sub> alkyl or halogen;

R<sub>2</sub> and R<sub>3</sub> are both hydrogen;

R<sub>8</sub> is C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl(C<sub>1</sub>-C<sub>3</sub>)alkyl, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>2</sub> alkyl), or -N(C<sub>1</sub>-C<sub>2</sub> alkyl)SO<sub>2</sub>(C<sub>1</sub>-C<sub>2</sub> alkyl); and

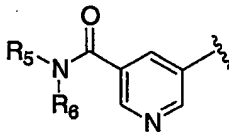
10 R<sub>f</sub> and R<sub>g</sub> are independently halogen.

Preferably R<sub>1</sub> in compounds of formula Z27 is ethyl. More

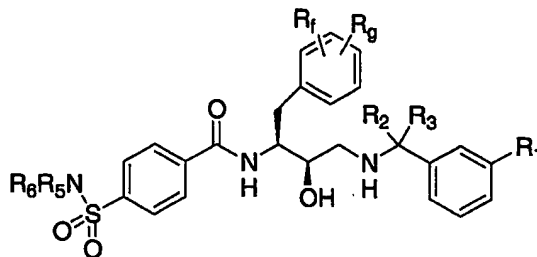
preferably, Z is .

Equally preferably, R<sub>8</sub> is C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl(C<sub>1</sub>-C<sub>3</sub>)alkyl, -NHSO<sub>2</sub>CH<sub>3</sub>, or -NCH<sub>3</sub>SO<sub>2</sub>CH<sub>3</sub>.

15 Other preferred compounds include those wherein Z is pyridyl substituted with C(O)NR<sub>5</sub>R<sub>6</sub>, wherein R<sub>5</sub> and R<sub>6</sub> are independently C<sub>3</sub>-C<sub>4</sub> alkyl; or R<sub>5</sub> is methyl or ethyl and R<sub>6</sub> is C<sub>3</sub> alkyl. More preferably, R<sub>5</sub> and R<sub>6</sub> are propyl. Still more

preferably, Z is  or the N-oxide thereof.

20 Other preferred compounds of the invention are those of formula Z28



Z28

or a pharmaceutically acceptable salt thereof, wherein

$R_1$  is  $C_2$ - $C_3$  alkyl;

$R_2$  and  $R_3$  are both hydrogen;

$R_5$  and  $R_6$  independently represent (a)  $C_1$ - $C_3$  alkyl optionally substituted with phenyl and (b) phenyl optionally

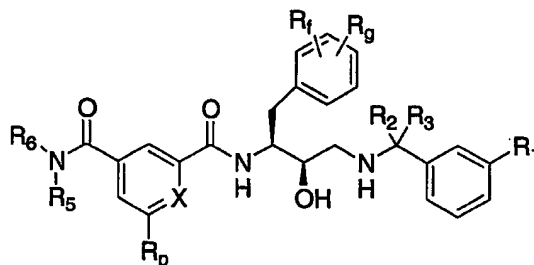
5 substituted with halogen; and

$R_f$  and  $R_g$  are independently halogen.

Preferred compounds of formula Z28 include those where  $R_5$  is methyl optionally substituted with phenyl and  $R_6$  is phenyl.

10 Other preferred compounds of formula Z28 include those where  $R_5$  is  $C_1$ - $C_2$  alkyl and  $R_6$  is 4-halophenyl, preferably 4-chlorophenyl.

Other preferred compounds of the invention are those of formula Z29



15

Z29

or a pharmaceutically acceptable salt thereof, wherein  $X$  is nitrogen or  $N^+-O^-$ ;

$R_1$  is  $C_2$ - $C_4$  alkynyl or  $C_1$ - $C_3$  alkyl;

20  $R_2$  and  $R_3$  are both hydrogen; or

$R_2$  and  $R_3$  together form a 3-membered ring with the carbon atom to which they are attached;

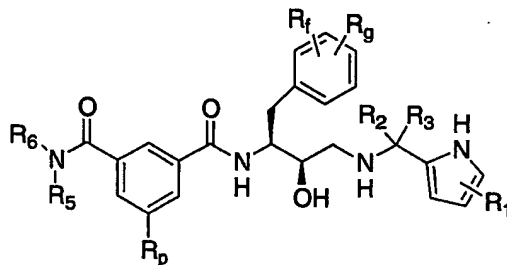
$R_f$  and  $R_g$  are independently halogen;

$R_p$  is hydrogen or  $C_1$ - $C_2$  alkyl; and

25  $R_5$  and  $R_6$  are independently  $C_3$ - $C_4$  alkyl.

Preferred compounds of formula Z29 include those where  $R_1$  is ethyl. More preferred compounds of formula Z29 include those where  $X$  is nitrogen;  $R_p$  is  $C_1$ - $C_2$  alkyl (preferably methyl); and  $R_1$  is ethyl.

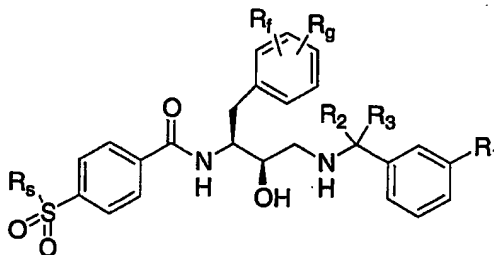
Other preferred compounds of the invention are those of formula Z30



Z30

- 5 or a pharmaceutically acceptable salt thereof, wherein  
 $R_1$  is hydrogen or  $C_1$ - $C_3$  alkyl;  
 $R_2$  and  $R_3$  are both hydrogen;  
 $R_p$  is  $C_1$ - $C_2$  alkyl;  
 $R_f$  and  $R_g$  are independently halogen; and  
 10  $R_5$  and  $R_6$  are independently  $C_3$ - $C_4$  alkyl.

Another preferred group of compounds of the invention is represented by formula Z31



Z31

- 15 or a pharmaceutically acceptable salt thereof, wherein  
 $R_s$  is  $NR_{s31}R_{s41}$  where  
 $R_{s31}$  is  $C_1$ - $C_2$  alkyl; and  
 $R_{s41}$  is  $C_1$ - $C_6$  alkyl, allyl, cyano( $C_1$ - $C_3$ )alkyl, ( $C_4$ -  
 $C_7$ )cycloalkyl, pyridyl( $C_1$ - $C_3$ )alkyl, phenyl, phenyl( $C_1$ -  
 20  $C_3$ )alkyl, amino( $C_1$ - $C_3$ )alkyl, mono( $C_1$ - $C_3$ )alkylamino( $C_1$ -  
 $C_2$ )alkyl, or di( $C_1$ - $C_3$ )alkylamino( $C_1$ - $C_2$ )alkyl; or  
 $R_s$  is  $CH_3$ ,  $-N(C_1$ - $C_2$  alkyl)phenyl, or  $-N(C_2$ - $C_3$  alkyl)( $C_3$ - $C_4$   
 alkyl);  
 $R_1$  is  $C_2$ - $C_3$  alkyl;  
 25  $R_2$  and  $R_3$  are both hydrogen; and

$R_f$  and  $R_g$  are independently halogen.

Preferred compounds of formula Z31 include those where  $R_{S41}$  is pyridylethyl or phenylethyl.

Other preferred compounds of Z31 are those where  $R_{S41}$  is diethylamino( $C_1$ - $C_2$ )alkyl, more preferably diethylaminomethyl.

Still other preferred compounds of Z31 are those where  $R_{S41}$  is  $C_{3-5}$  alkyl.

Particularly preferred compounds of formula Z31 include those where  $R_8$  is (2-cyanoethyl)(methyl)amino.

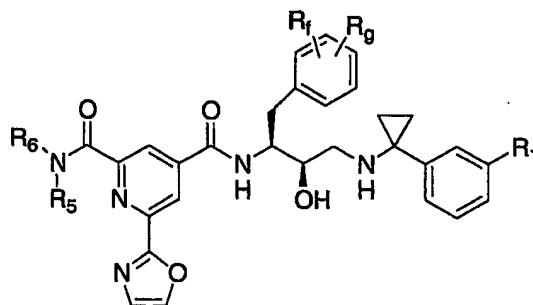
Other particularly preferred compounds of formula Z31 include those where  $R_8$  is (cyclohexyl)(methyl)amino.

In a preferred aspect of formula Z31,  $R_{S41}$  is  $C_1$ - $C_6$  alkyl, allyl, cyano( $C_1$ - $C_3$ )alkyl, ( $C_4$ - $C_7$ )cycloalkyl, pyridyl( $C_1$ - $C_3$ )alkyl, phenyl, or phenyl( $C_1$ - $C_3$ )alkyl.

In another preferred aspect of Z31,  $R_{S41}$  is phenyl or cyclohexyl.

In yet another preferred aspect of Z31,  $R_8$  is -N( $CH_3$ )phenyl, or -N(ethyl)( $C_3$ - $C_4$  alkyl).

Other preferred compounds of the invention are those of formula Z32



Z32

or a pharmaceutically acceptable salt thereof, wherein

$R_1$  is  $C_2$ - $C_3$  alkynyl or  $C_1$ - $C_3$  alkyl;

$R_f$  and  $R_g$  are independently halogen;

$R_5$  and  $R_6$  are independently  $C_1$ - $C_4$  alkyl.

Preferred compounds of formula Z33 include those where  $R_5$  and  $R_6$  are  $C_3$  alkyl.

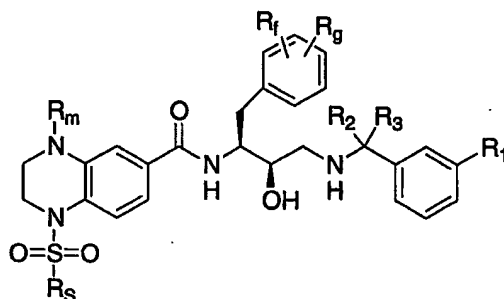
Other preferred compounds of formula Z33 include those where  $R_5$  is methyl and  $R_6$  is  $C_3$  alkyl.

Particularly compounds of formula Z33 include those where  $R_1$  is ethyl.

- 5 Other particularly preferred compounds of formula Z33 include those where  $R_5$  and  $R_6$  are both propyl or  $R_5$  is methyl and  $R_6$  is propyl, hereinafter Z33-1.

Still other preferred compounds of formula Z33 and Z33-1 include those wherein  $R_1$  is  $C_2$ - $C_3$  alkynyl (preferably  $C_2$  alkynyl).

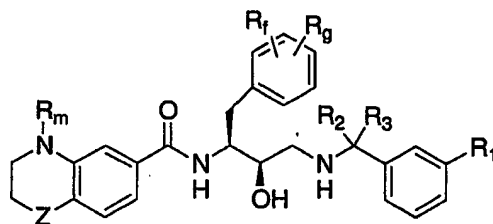
Other preferred compounds of the invention are those of formula Z33



Z33

- 15 or a pharmaceutically acceptable salt thereof, wherein  
 $R_5$  is  $C_1$ - $C_4$  alkyl;  
 $R_m$  is  $C_1$ - $C_4$  alkyl;  
 $R_1$  is  $C_2$ - $C_3$  alkyl;  
 $R_2$  and  $R_3$  are both hydrogen; and  
 20  $R_f$  and  $R_g$  are independently halogen.

Other preferred compounds of the invention are those of formula Z34



Z34

- 25 or a pharmaceutically acceptable salt thereof, wherein

$R_m$  is  $C_1$ - $C_4$  alkyl;

$R_1$  is  $C_2$ - $C_3$  alkyl;

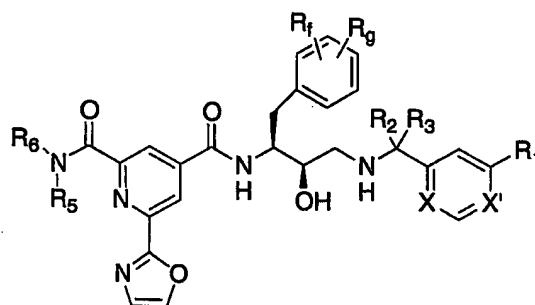
$R_2$  and  $R_3$  are both hydrogen; and

$R_f$  and  $R_g$  are independently halogen;

5  $Z$  is  $S$ ,  $S(O)$ ,  $S(O)_2$ , or  $O$ .

Preferred compounds of formula Z34 include those where  $Z$  is  $S$  or  $S(O)$ . More preferably,  $R_1$  is  $C_2$  alkyl.

Other preferred compounds of the invention are those of  
10 formula Z35



Z35

or a pharmaceutically acceptable salt thereof, wherein one of  $X$  and  $X'$  is  $CH$  and the other is  $N$ ;

15  $R_1$  is  $C_2$ - $C_4$  alkynyl; amino( $C_1$ - $C_3$ )alkyl, mono( $C_1$ - $C_3$ )alkylamino( $C_1$ - $C_2$ )alkyl, or di( $C_1$ - $C_3$ )alkylamino( $C_1$ - $C_2$ )alkyl;

$R_2$  and  $R_3$  are both hydrogen; or

$R_2$  and  $R_3$  together form a 3-membered ring with the carbon atom to which they are attached;

20  $R_f$  and  $R_g$  are independently halogen;

$R_5$  and  $R_6$  are independently  $C_1$ - $C_3$ - $C_4$  alkyl.

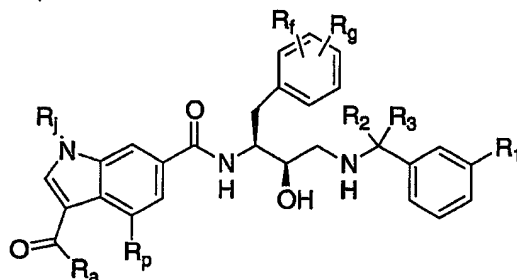
Preferred compounds of formula Z35 include those where  $R_2$  and  $R_3$  together form a 3-membered ring with the carbon atom to which they are attached;  $X$  is  $N$ ; and  $X'$  is  $CH$ , hereinafter Z35-1.  
25 1.

Other preferred compounds of formula Z35 include those of formula Z35-1, i.e., compounds of Z35 where  $R_2$  and  $R_3$  are hydrogen;  $X'$  is  $N$ ; and  $X$  is  $CH$ , hereinafter Z35-2.



More preferred compounds of Z35, Z35-1, and Z35-2 include those where  $R_1$  is  $C_2$  alkynyl. More preferably,  $R_1$  is also di( $C_1$ - $C_3$ )alkylamino( $C_1$ - $C_3$ )alkyl. Even more preferably,  $R_1$  is dimethylamino( $C_1$ - $C_2$ )alkyl.

- 5 Other preferred compounds of the invention are those of formula Z36



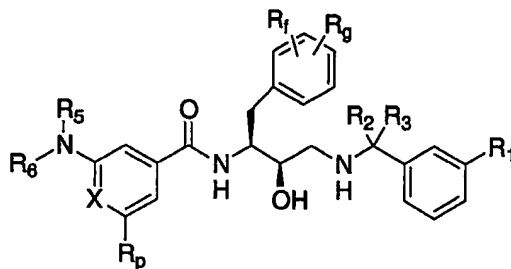
Z36

- or a pharmaceutically acceptable salt thereof, wherein
- 10  $R_1$  is  $C_2$ - $C_3$  alkyl,;
- $R_2$  and  $R_3$  are both hydrogen;
- $R_f$  and  $R_g$  are independently halogen;
- $R_p$  is hydrogen, cyano,  $C_1$ - $C_3$  alkyl, amino,  $N$ -( $C_1$ - $C_3$  alkylsulfonyl)- $N$ -(( $C_1$ - $C_3$ )alkyl)amino, 2-oxazolyl, or 1-
- 15 pyrrolyl optionally substituted in the 2 and 5 positions with  $C_1$ - $C_2$  alkyl;
- $R_a$  is  $C_1$ - $C_3$  alkyl, H or trifluoromethyl; and
- $R_j$  is  $C_1$ - $C_5$  alkyl.

- 20 Preferred compounds of Z36 include those where  $R_j$  is methyl or ethyl and  $R_p$  is hydrogen, methyl, or ethyl.

Other preferred compounds of Z36 include those where  $R_j$  is methyl and  $R_p$  is hydrogen.

- Other preferred compounds of the invention are those of
- 25 formula Z37



Z37

or a pharmaceutically acceptable salt thereof, wherein  
X is nitrogen or  $N^+-O^-$ ;

- 5  $R_1$  is  $C_2-C_4$  alkynyl, cyano,  $C_1-C_3$  alkyl, or  $CF_3$ ;
- $R_2$  and  $R_3$  are both hydrogen; or
- $R_2$  and  $R_3$  together form a 3-membered ring with the carbon atom to which they are attached;
- $R_f$  and  $R_g$  are independently halogen;
- 10  $R_p$  is hydrogen, cyano or  $C_1-C_2$  alkyl; and
- $R_5$  and  $R_6$  are independently  $C_1-C_4$  alkyl.

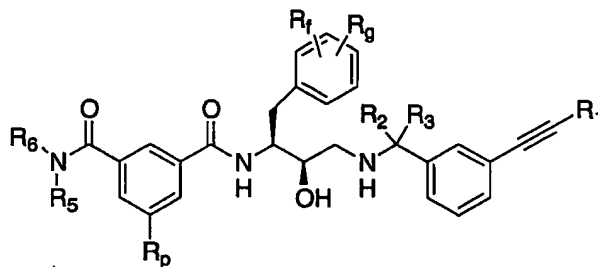
Preferred compounds of formula Z37 include those of formula Z37-1, i.e., compounds of Z37 where X is N. Preferred compounds of Z37-1 include those where  $R_p$  is cyano. More preferred compounds of Z37-1 are those where  $R_5$  is methyl and  $R_6$  is  $C_2-C_4$  alkyl. Particularly preferred compounds of Z37-1 are those where  $R_6$  is propyl.

Other preferred compounds of formula Z37 include those wherein  $R_1$  is  $C_2-C_3$  alkyl;  $R_p$  is methyl or ethyl; and  $R_5$  and  $R_6$  are independently  $C_3-C_4$  alkyl. More preferably,  $R_2$  and  $R_3$  are also hydrogen.

Other preferred compounds of Z37 include those wherein  $R_1$  is  $C_2-C_3$  alkynyl, or  $C_2$  alkyl; and  $R_p$  is methyl.

Still other preferred compounds of Z37 include those wherein  $R_1$  is  $CF_3$ . More preferably,  $R_p$  is also methyl. Even more preferably X is CH.

Other preferred compounds of the invention are those of formula Z38



Z38

or a pharmaceutically acceptable salt thereof, wherein

R<sub>1</sub> is hydrogen, methyl, or -CH<sub>2</sub>OH;

5 R<sub>2</sub> and R<sub>3</sub> are both hydrogen; or

R<sub>2</sub> and R<sub>3</sub> together with the carbon atom to which they are attached form a 3-membered ring;

R<sub>p</sub> is C<sub>2</sub>-C<sub>3</sub> alkynyl or C<sub>1</sub>-C<sub>3</sub> alkyl;

R<sub>f</sub> and R<sub>g</sub> are independently halogen;

10 R<sub>5</sub> and R<sub>6</sub> are independently C<sub>3</sub>-C<sub>4</sub> alkyl, or

R<sub>5</sub> is methyl and R<sub>6</sub> is C<sub>3</sub>-C<sub>4</sub> alkyl.

In preferred compounds of Formula Z38 include those wherein R<sub>p</sub> is methyl, hereinafter Z38-1.

Other preferred compounds of Formula Z38 include those  
15 wherein R<sub>p</sub> is C<sub>2</sub> alkynyl, hereinafter Z38-2.

Other preferred compounds of Z38, Z38-1, and Z38-2 include those wherein R<sub>1</sub> is hydrogen and R<sub>2</sub> and R<sub>3</sub> are both hydrogen, hereinafter Z38-3. Preferred compounds of Z38-3 include those wherein R<sub>5</sub> and R<sub>6</sub> are both C<sub>3</sub>-C<sub>4</sub> alkyl. Even more preferably,  
20 both are C<sub>3</sub> alkyl.

Still other preferred compounds of Z38, Z38-1, and Z38-2 include those wherein R<sub>1</sub> is hydrogen and R<sub>2</sub> and R<sub>3</sub> form a 3-membered ring, hereinafter Z38-4.

Other preferred compounds of Z38, Z38-1, and Z38-2 include  
25 those wherein R<sub>1</sub> is -CH<sub>2</sub>OH. Preferably, R<sub>2</sub> and R<sub>3</sub> are also hydrogen, hereinafter Z38-4A.

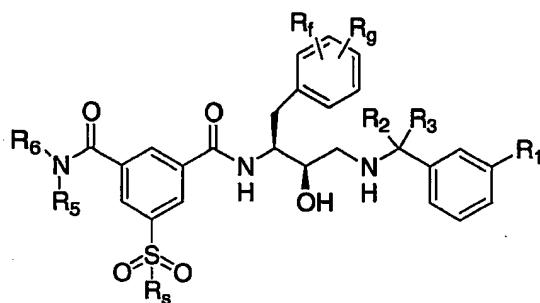
Even more preferred compounds of Z38 are those where R<sub>1</sub> is hydrogen and R<sub>2</sub> and R<sub>3</sub> together with the carbon atom to which they are attached form a 3-membered ring, hereinafter Z38-5.

Preferred compounds of formula Z38-5 include those wherein  $R_p$  is  $C_2$ - $C_3$  alkynyl (preferably  $C_2$  alkynyl) or methyl. More preferably, at least one of  $R_5$  and  $R_6$  is  $C_3$  alkyl. Still more preferably,  $R_5$  is methyl or propyl and  $R_6$  is propyl,

5 hereinafter Z38-5A.

Still other preferred Z38, Z38-1, Z38-2, Z38-3, Z38-4, Z38-4A, Z38-5 and Z38-5A include compounds are those where  $R_f$  and  $R_g$  are both chloro or fluoro. Particularly preferred among Z38 compounds are those where  $R_f$  and  $R_g$  are both fluoro and are in the 3 and 5 positions with respect to the point of attachment of the phenyl group.

Other preferred compounds of the invention are those of formula Z39



Z39

wherein

$R_1$  is  $C_2$ - $C_3$  alkyl;

$R_2$  and  $R_3$  are both methyl or

$R_2$ ,  $R_3$ , and the carbon to which they are attached form a

20 cyclopropyl ring;

$R_f$  and  $R_g$  are independently halogen;

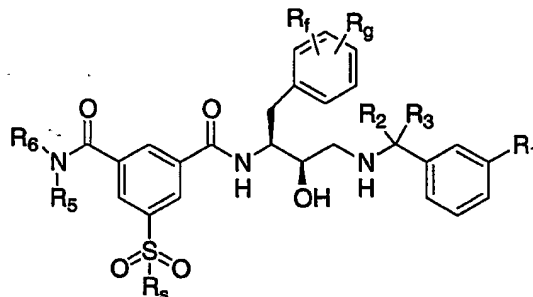
$R_5$  and  $R_6$  are independently  $C_3$ - $C_4$  alkyl; and

$R_8$  is  $-NH(C_1$ - $C_4$  hydroxyalkyl).

Preferred compounds of Z39 include those wherein the hydroxyalkyl group is 2-hydroxy-1,1-dimethylethyl. More preferably,  $R_1$  is also ethyl.

Preferably  $R_2$  and  $R_3$  are both methyl. Equally preferably,  $R_2$ ,  $R_3$ , and the carbon to which they are attached form a cyclopropyl ring.

Other preferred compounds of the invention are those of formula Z40



Z40

5 wherein

R<sub>1</sub> is C<sub>2</sub>-C<sub>3</sub> alkynyl;

R<sub>2</sub> and R<sub>3</sub> are both hydrogen; or

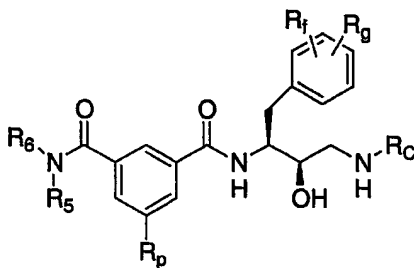
R<sub>f</sub> and R<sub>g</sub> are independently halogen;

R<sub>5</sub> and R<sub>6</sub> are independently C<sub>3</sub>-C<sub>4</sub> alkyl; and

10 R<sub>8</sub> is -NH(C<sub>2</sub>-C<sub>4</sub> hydroxyalkyl).

Preferred compounds of Z40 include those wherein the hydroxyalkyl group is 2-hydroxy-1,1-dimethylethyl; or 2-hydroxyethyl.

Other preferred compounds of the invention are those of  
15 formula Z41



Z41

wherein,

R<sub>c</sub> is C<sub>4</sub>-C<sub>5</sub> alkyl; cyclopropyl; tetrahydronaphthyl; -CH(C<sub>2</sub> alkyl-S-(C<sub>1</sub>-C<sub>2</sub>) alkyl)C(O)NH(C<sub>4</sub> alkyl); -CH(C<sub>2</sub> alkyl-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>2</sub>) alkyl)C(O)NH(C<sub>4</sub> alkyl); pyrimidyl optionally substituted with C<sub>3</sub>-C<sub>4</sub> alkyl; thiochroman 1,1-dioxide; -CH<sub>2</sub>-thiazolyl optionally substituted with C<sub>3</sub>-C<sub>4</sub> alkyl, or -CH<sub>2</sub>-isoxazolyl optionally substituted with C<sub>1</sub>-C<sub>5</sub> alkyl;

R<sub>f</sub> and R<sub>g</sub> are independently halogen;

R<sub>p</sub> is -NHSO<sub>2</sub>CF<sub>3</sub>, -SO<sub>2</sub>NH(C<sub>3</sub>-C<sub>4</sub> hydroxyalkyl), -NHSO<sub>2</sub>CH<sub>3</sub>, oxazol-2-yl, or C<sub>2</sub>-C<sub>4</sub> alkynyl; and

R<sub>5</sub> and R<sub>6</sub> are independently C<sub>3</sub>-C<sub>4</sub> alkyl.

5 Preferred compounds of Z41 include those wherein

R<sub>c</sub> is C<sub>4</sub>-C<sub>5</sub> alkyl (preferably isobutyl or isopentyl);

cyclopropyl; tetrahydronaphthylenyl; -CH(C<sub>2</sub> alkyl-S-(C<sub>1</sub>-C<sub>2</sub>)

alkyl)C(O)NH(C<sub>4</sub> alkyl); -CH(C<sub>2</sub> alkyl-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>2</sub>) alkyl)C(O)NH(C<sub>4</sub>

alkyl); pyrimidyl optionally substituted with C<sub>3</sub>-C<sub>4</sub> alkyl;

10 thiochroman 1,1-dioxide; -CH<sub>2</sub>-thiazolyl optionally substituted with C<sub>3</sub>-C<sub>4</sub> alkyl, hereinafter Z41-1.

More Preferred compounds of Z41-1 include those wherein

R<sub>c</sub> is isobutyl; 1,2,3,4-tetrahydronaphthylen-1-yl, -CH(CH<sub>2</sub>CH<sub>2</sub> - S-CH<sub>3</sub>)C(O)NH(C<sub>1</sub>-C<sub>5</sub> alkyl) where the alkyl group is preferably

15 isobutyl, or 2-tert butylpyrimidin-4-yl, hereinafter Z41-2.

Other preferred compounds of Z41 include those wherein

R<sub>p</sub> is -SO<sub>2</sub>NH(2-hydroxy-1,1-dimethylethyl), hereinafter z41-3.

Other preferred compounds of Z41, Z41-1, Z41-2, and Z41-3 include those wherein R<sub>5</sub> and R<sub>6</sub> are both C<sub>3</sub> alkyl.

20 Other preferred compounds of Z41 include those wherein

R<sub>p</sub> is oxazol-2-yl; and R<sub>c</sub> is -CH<sub>2</sub>-(2-isobutylthiazol-5-yl).

Still other preferred compounds of Z41 include those

wherein R<sub>p</sub> is C<sub>2</sub>-C<sub>3</sub> alkynyl (preferably C<sub>2</sub> alkynyl) and R<sub>c</sub> is -CH<sub>2</sub>-(2-isobutylthiazol-5-yl).

25 Yet other preferred compounds of formula Z41 include those

wherein R<sub>p</sub> is -CH<sub>2</sub>-isoxazolyl optionally substituted with C<sub>1</sub>-C<sub>5</sub>

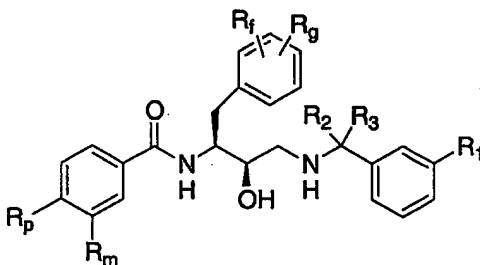
alkyl. More preferably, R<sub>p</sub> is -CH<sub>2</sub>-isoxazol-5-yl. Even more

preferably, it is -CH<sub>2</sub>-(3-isobutylisoxazol-5-yl). Even more

preferably R<sub>p</sub> is also C<sub>2</sub>-C<sub>3</sub> alkynyl. Still more preferably R<sub>5</sub>

30 and R<sub>6</sub> are both C<sub>3</sub> alkyl.

Other preferred compounds of the invention are those of formula Z42



Z42

wherein

R<sub>1</sub> is C<sub>2</sub>-C<sub>3</sub> alkyl, or halogen;

5 R<sub>2</sub> and R<sub>3</sub> are both hydrogen; or

R<sub>2</sub>, R<sub>3</sub>, and the carbon to which they are attached form a cyclopropyl ring;

R<sub>f</sub> and R<sub>g</sub> are independently halogen; and

R<sub>m</sub> is -NH-SO<sub>2</sub>CF<sub>3</sub>, oxazol-2-yl, -N(CH<sub>3</sub>)SO<sub>2</sub>CH<sub>3</sub>, -N(C<sub>3</sub>-C<sub>4</sub>

10 hydroxyalkyl)SO<sub>2</sub>(C<sub>1</sub>-C<sub>2</sub> alkyl), and R<sub>p</sub> is H; or

R<sub>m</sub> is H and R<sub>p</sub> is -NH-SO<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>SO<sub>2</sub>(C<sub>1</sub>-C<sub>2</sub> alkyl) where the alkyl group is preferably methyl; or

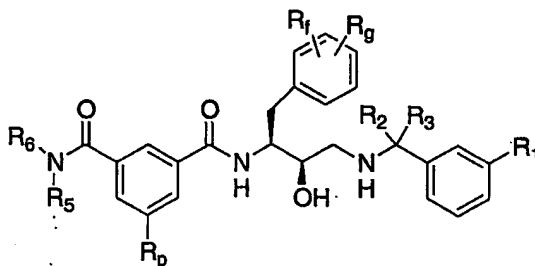
R<sub>m</sub> is -C(O)pyrrolidinyl and R<sub>p</sub> is OH.

Preferred compounds of formula Z42 include those wherein

15 R<sub>m</sub> is H and R<sub>p</sub> is -NH-SO<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>SO<sub>2</sub>(C<sub>1</sub>-C<sub>2</sub> alkyl), hereinafter Z42-1. Also preferred are compounds of Z42 wherein R<sub>m</sub> is -NH-SO<sub>2</sub>CF<sub>3</sub>, oxazol-2-yl, -N(CH<sub>3</sub>)SO<sub>2</sub>CH<sub>3</sub>, -N(C<sub>3</sub>-C<sub>4</sub> hydroxyalkyl)SO<sub>2</sub>(C<sub>1</sub>-C<sub>2</sub> alkyl), and R<sub>p</sub> is H, hereinafter Z42-2.

Preferred compounds of Z42, Z42-1, and Z42-2 include those  
20 wherein R<sub>1</sub> is ethyl, bromo, or iodo. More preferred is when R<sub>2</sub> and R<sub>3</sub> are also both hydrogen;

Other preferred compounds of the invention are those of formula Z43



Z43

wherein

- $R_1$  is  $C_2$ - $C_5$  alkyl,  $C_3$ - $C_6$  cyanoalkyl,  $C_3$ - $C_6$  alkenyl,  $-NHSO_2(C_1$ - $C_2$  alkyl),  $C_4$ - $C_5$  haloalkyl,  $-C_3$  alkyl- $CO_2$ -( $C_1$ - $C_2$  alkyl), CN,  $-N(C_1$ - $C_2$  alkyl) $SO_2(C_1$ - $C_2$  alkyl),  $-SO_2(C_1$ - $C_2$  alkyl),  $-S(O)(C_1$ - $C_6$  alkyl),  $-NH-(C_3$ - $C_6$  cycloalkyl), or  $-OC(O)N(C_1$ - $C_2$  alkyl)( $C_1$ - $C_2$  alkyl),
- $R_2$  and  $R_3$  are both hydrogen;
- $R_f$  and  $R_g$  are independently halogen;
- $R_p$  is  $C_1$ - $C_2$  alkyl;
- $R_5$  and  $R_6$  are independently  $C_3$ - $C_5$  alkyl,  $C_1$ - $C_2$  alkoxy  $C_1$ - $C_3$  alkyl, or  $C_3$ - $C_5$  alkenyl (preferably  $C_3$  alkenyl) or
- $R_5$  is H and  $R_6$  is  $C_4$ - $C_6$  alkyl or  $(C_1$ - $C_2$  alkoxy)-( $C_2$ - $C_3$  alkyl),;
- $R_5$  is ethyl and  $R_6$  is  $C_2$ - $C_3$  hydroxyalkyl or  $-(C_1$ - $C_2$  alkyl)- $N(C_1$ - $C_2$  alkyl)( $C_1$ - $C_2$  alkyl); or
- $R_5$  is  $CH_3$  and  $R_6$  is  $C_4$ - $C_5$  alkyl, cyclohexyl,  $-(C_1$ - $C_2$  alkyl)-phenyl,  $-(C_1$ - $C_2$  alkyl)-pyridyl, or  $-CH_2$ -furyl; or
- $R_5$  is methyl or ethyl and  $R_6$  is  $(C_1$ - $C_2$  alkoxy)-( $C_2$ - $C_3$  alkyl) or  $-CH_2$ -( $C_3$ - $C_6$  cycloalkyl), or
- $R_5$ ,  $R_6$ , and the nitrogen to which they are attached form a piperidinyll ring optionally substituted with  $C_3$ - $C_4$  alkyl or OH, azepanyl, pyrrolidine-2-carboxylic acid amide, 3-hydroxypiperidin-1-yl.

- Preferred compounds of formula Z43 include those wherein
- $R_1$  is  $C_2$ - $C_4$  alkyl, hereinafter Z43-1. Preferably,  $R_1$  is ethyl, isopropyl, isobutyl, sec-butyl, or isopentyl. More preferably ethyl or isopropyl. Still more preferably ethyl.

- Other preferred compounds of formula Z43 and Z43-1 include those wherein  $R_5$  and  $R_6$  are simultaneously ethoxyethyl
- (hereinafter Z43-1A),  $R_5$  is propyl and  $R_6$  is butyl (hereinafter Z43-1B),  $R_5$  is ethyl and  $R_6$  is butyl (hereinafter Z43-1C),  $R_5$  is methyl or ethyl and  $R_6$  is  $-CH_2$ -(cyclopropyl), isobutyl, or  $C_2$ - $C_4$  alkynyl (hereinafter Z43-1D), or  $R_5$  is ethyl and  $R_6$  is propyl



(hereinafter Z43-1E), or  $R_5$  is hydrogen and  $R_6$  is sec-butyl (hereinafter Z43-1F).

Even more preferred compounds of Z43, Z43-1, Z43-1A, Z43-1B, Z43-1C, Z43-1D, Z43-1E and Z43-1F are those wherein  $R_p$  is methyl or  $C_2$  alkynyl.

Other preferred compounds of formula Z43 include those wherein  $R_5$ ,  $R_6$ , and the nitrogen to which they are attached form a 2-propyl piperidin-1-yl ring.

Still other preferred compounds of formula Z43 include those wherein  $R_1$  is cyclopentyl, cyclohexyl, propenyl, allyl, or  $-(C_3-C_6 \text{ alkyl})-CN$ , 4-chlorobutyl, 3-pyridyl, methyl 2-methylpropanoate, hex-5-enyl, CN,  $-N(CH_3)SO_2CH_3$ ,  $-SO_2CH_2CH_3$ , 3-methylpyrid-2-yl, oxazol-2-yl, 3,5-dimethylisoxazol-4-yl, 3-methylthien-2-yl, 2-pyridyl, 4-carbaldehydefuran-5-yl, and 2-carbaldehydethien-5-yl, 2-carbaldehyde-3-methylthien-5-yl, 2-methoxypyridin-4-yl,  $-NH$ -cyclopropyl,  $-NHSO_2CH_3$ ; and  $R_p$  is methyl, hereinafter Z43-2. Preferred compounds of formula Z43-2 include those wherein  $R_5$  and  $R_6$  are also both  $C_3$  alkyl. Also preferred is when  $R_5$  is ethyl and  $R_6$  is butyl.

Preferred compounds of Z43, Z43-1, and Z43-2 include those wherein  $R_1$  is  $C_2-C_3$  alkynyl (preferably  $C_2$  alkynyl), hereinafter Z43-3.

Preferred compounds of Z43, Z43-1, Z43-2, and Z43-3 include those wherein  $R_5$  and  $R_6$  are independently  $C_3-C_5$  alkyl,  $C_1-C_2$  alkoxy  $C_1-C_3$  alkyl. Other preferred compounds of Z43, Z43-1, Z43-2, and Z43-3 include those wherein  $R_5$  is H and  $R_6$  is  $C_{4,5}-C_6$  alkyl or  $(C_1-C_2 \text{ alkoxy})-(C_2-C_3 \text{ alkyl})$ . Still other preferred compounds of Z43, Z43-1, Z43-2, and Z43-3 include those wherein  $R_5$  is ethyl and  $R_6$  is  $C_2-C_3$  hydroxyalkyl or  $-(C_1-C_2 \text{ alkyl})-N(C_1-C_2 \text{ alkyl})(C_1-C_2 \text{ alkyl})$ . More preferably, the  $-(C_1-C_2 \text{ alkyl})-N(C_1-C_2 \text{ alkyl})(C_1-C_2 \text{ alkyl})$  is  $-(C_1-C_2 \text{ alkyl})-N(CH_3)_2$ .

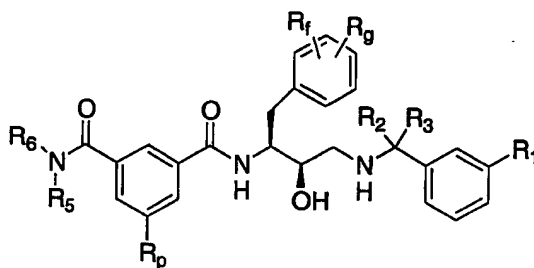
Yet still other preferred compounds of Z43, Z43-1, Z43-2, and Z43-3 include those wherein  $R_5$  is  $CH_3$  and  $R_6$  is  $C_4-C_5$  alkyl, cyclohexyl,  $-(C_1-C_2 \text{ alkyl})$ -phenyl,  $-(C_1-C_2 \text{ alkyl})$ -pyridyl, or -

CH<sub>2</sub>-furyl. Preferably, R<sub>5</sub> is CH<sub>3</sub> and R<sub>6</sub> is C<sub>4</sub>-C<sub>5</sub> alkyl, hereinafter Z43-4. Still yet other preferred compounds of Z43, Z43-1, Z43-2, and Z43-3 include those wherein R<sub>5</sub> is methyl or ethyl and R<sub>6</sub> is (C<sub>1</sub>-C<sub>2</sub> alkoxy)-(C<sub>2</sub>-C<sub>3</sub> alkyl).

5 Other preferred compounds of Z43, Z43-1, Z43-2, and Z43-3 include those wherein R<sub>5</sub>, R<sub>6</sub>, and the nitrogen to which they are attached form a piperidinyl ring optionally substituted with C<sub>3</sub>-C<sub>4</sub> alkyl or OH, azepanyl, pyrrolidine-2-carboxylic acid amide, or 3-hydroxypiperidin-1-yl.

10 Further preferred compounds Z43, Z43-1, Z43-2, Z43-3, and Z43-4 include those wherein R<sub>p</sub> is methyl.

Other preferred compounds of the invention are those of formula Z44



Z44

15 wherein

R<sub>1</sub> is C<sub>2</sub>-C<sub>3</sub> alkyl, halogen, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl) preferably the cycloalkyl group is a cyclopropyl group,

R<sub>f</sub> and R<sub>g</sub> are independently halogen;

20 R<sub>p</sub> is C<sub>1</sub>-C<sub>2</sub> alkyl, oxazolyl, thiazolyl, or C<sub>2</sub>-C<sub>3</sub> alkynyl;

R<sub>2</sub>, R<sub>3</sub>, and the carbon to which they are attached form a cyclopropyl ring; or

R<sub>2</sub> and R<sub>3</sub> are both methyl;

R<sub>5</sub> and R<sub>6</sub> are independently C<sub>3</sub>-C<sub>4</sub> alkyl; or

25 R<sub>5</sub> is methyl and R<sub>6</sub> is C<sub>3</sub>-C<sub>5</sub> alkyl.

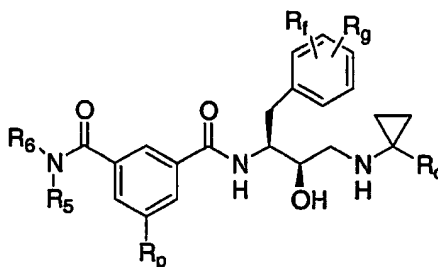
Preferred compounds of formula Z44 include those wherein R<sub>2</sub> and R<sub>3</sub> are both methyl; and R<sub>5</sub> and R<sub>6</sub> are independently C<sub>3</sub>-C<sub>4</sub> alkyl, hereinafter Z44-1.

Preferred compounds of formula Z44 and Z44-1 include those wherein  $R_p$  is oxazol-2-yl or thiazol-2-yl.

Preferred compounds of formula Z44 include those wherein  $R_p$  is  $C_2$ - $C_3$  alkynyl; and  $R_5$  and  $R_6$  are independently  $C_3$ - $C_4$  alkyl.

Also preferred are compounds wherein  $R_1$  is bromo, chloro, or iodo or  $-NH(\text{cyclopropyl})$ .

Other preferred compounds of the invention are those of formula Z45



Z45

wherein

$R_c$  is isoxazolyl optionally substituted with  $C_3$ - $C_5$  alkyl, thiazolyl optionally substituted with  $C_3$ - $C_4$  alkyl, or  $-C_1$ - $C_3$  alkyl- $C(O)NH(C_1$ - $C_3$  alkyl);

$R_f$  and  $R_g$  are independently halogen;

$R_p$  is  $C_1$ - $C_2$  alkyl, oxazolyl, thiazolyl, or  $C_2$ - $C_4$  alkynyl;

$R_5$  and  $R_6$  are independently  $C_3$ - $C_4$  alkyl.

Preferred compounds of formula Z45 include those wherein  $R_p$  is oxazol-2-yl or thiazol-2-yl, hereinafter Z45-1. More

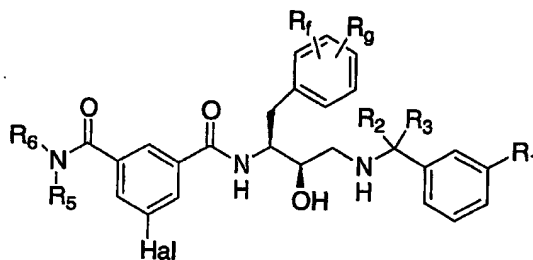
preferred compounds of Z45-1 include those wherein  $R_c$  is 3-isobutylisoxazol-5-yl or N-isobutyl-2-methylpropion-2-yl amide; and  $R_f$  and  $R_g$  are independently Cl or F.

Other preferred compounds of formula Z45 include those wherein  $R_c$  is 2-isobutylthiazol-2-yl; and  $R_f$  and  $R_g$  are

independently Cl or F.

Still other preferred compounds of formula Z45 include those wherein  $R_c$  is 3-isobutylisoxazol-5-yl or N-isobutyl-2-methylpropion-2-yl amide;  $R_f$  and  $R_g$  are independently Cl or F; and  $R_p$  is  $C_2$ - $C_3$  alkynyl.

Other preferred compounds of the invention are those of formula Z46

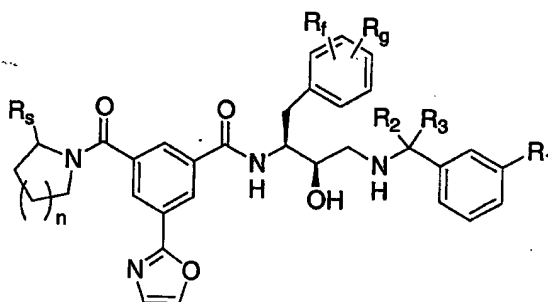


Z46

- 5 wherein  
 Hal is a halogen;  
 $R_1$  is  $C_1$ - $C_2$  alkyl, or halogen;  
 $R_2$  and  $R_3$  are both hydrogen;  
 $R_f$  and  $R_g$  are independently halogen;  
 10  $R_z$  is  $C_1$ - $C_2$  alkyl;  
 $R_5$  and  $R_6$  are independently  $C_3$ - $C_4$  alkyl.

Preferred compounds of formula Z45 include those wherein  
 Hal is bromo or chloro. More preferably,  $R_1$  is also methyl,  
 ethyl, bromo or iodo. More preferably  $R_1$  is methyl or ethyl.  
 15 Even more preferably, it is ethyl.

Other preferred compounds of the invention are those of  
 formula Z47

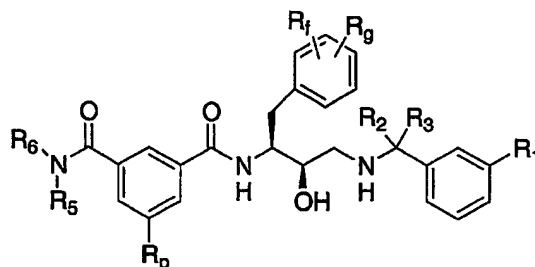


Z47

- 20  $n$  is 0, 1 or 2;  
 $R_1$  is  $C_1$ - $C_2$  alkyl;  
 $R_2$  and  $R_3$  are both hydrogen;  
 $R_f$  and  $R_g$  are independently halogen;  
 $R_s$  is  $(C_1$ - $C_2$  alkoxy)-(C1-C2 alkyl).

Preferred compounds of Z47 include those wherein  $R_s$  is methoxymethyl. Preferably  $n$  is 1.

Other preferred compounds of the invention are those of formula Z48



Z48

wherein

$R_1$  is  $C_1$ - $C_2$  alkyl;

$R_2$  and  $R_3$  are both hydrogen;

10  $R_f$  and  $R_g$  are independently halogen;

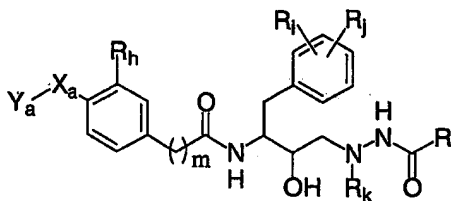
$R_p$  is isoxazole optionally substituted with  $C_1$ - $C_2$  alkyl;

$R_5$  and  $R_6$  are independently  $C_3$ - $C_4$  alkyl.

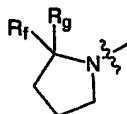
Preferred compounds of formula Z48 include those wherein  $R_p$  is 3-methylisoxazol-4-yl, 5-oxazolyl, 3-oxazolyl, 3-methyloxazol-2-yl, 3-ethyloxazol-2-yl.

Preferred compounds of  $Z_1$ - $Z_{48}$  include those wherein at least one of  $R_f$  and  $R_g$  is fluoro. More preferably, both are fluoro. Even more preferably,  $R_f$  and  $R_g$  are in the 3 and 5 positions with respect to the point of attachment of the phenyl group.

In another aspect, the invention includes compounds of the formula Z49:



Z49



wherein Ya is or  $-N(CH_2CH_2CH_3)_2$ ;

$R_f$  and  $R_g$  are both hydrogen or taken together with the carbon to which they are attached form a carbonyl;

$X_a$  is a covalent bond or a carbonyl;

5  $R_h$  is hydrogen or hydroxy;

$R_i$  and  $R_j$  are independently hydrogen or a halogen selected from Br, F, Cl or I;

$R_k$  is  $-C_{1-6}$  alkyl;

10  $R_l$  is  $-C_{1-6}$  alkyl or phenyl optionally substituted with  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, halogen, hydroxy, amino, mono( $C_{1-6}$ )alkylamino, di( $C_{1-6}$ )alkylamino, trifluoromethyl; and m is 0 or 1.

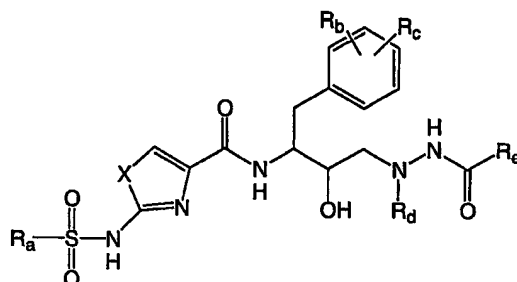
In this embodiment,  $R_f$  and  $R_g$  preferably are taken together with the carbon to which they are attached to form a carbonyl,  $X_a$  is preferably a covalent bond,  $R_h$  is preferably hydrogen, m is preferably 1, and  $R_i$  and  $R_j$  are preferably hydrogen. More preferably,  $R_k$  is ethyl and  $R_e$  is a meta-substituted ethyl phenyl group,  $-CH_2CH_2CH(CH_3)_2$ , methyl or phenyl.  $R_l$  is preferably phenyl.

20 In another preferred aspect of Z49,  $R_f$  and  $R_g$  are hydrogen,  $X_a$  is a carbonyl,  $R_h$  is hydroxyl,  $R_i$  and  $R_j$  are hydrogen and  $R_k$  is ethyl. In another aspect, and in accordance with these preferred groups,  $R_e$  is preferably a meta-substituted ethyl phenyl group,  $-CH_2CH_2CH(CH_3)_2$ , or a methyl group.

25 In accordance with this embodiment,  $R_a$  is preferably methyl and  $R_d$  is preferably ethyl, X is preferably O, and  $R_b$  and  $R_c$  are preferably hydrogen. In another aspect, and in accordance with these preferred groups,  $R_e$  is preferably a meta-substituted ethyl phenyl group,  $-CH_2CH_2CH(CH_3)_2$ , methyl or phenyl. Alternatively, and in accordance with this embodiment, X is preferably S,  $R_b$  and  $R_c$  are hydrogen, and  $R_e$  is a meta-

substituted ethyl phenyl group or a methyl group.  $R_e$  is preferably phenyl.

In another aspect, the invention provides compounds of the formula Z50:



Z50

wherein

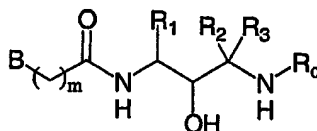
$R_a$  and  $R_d$  are  $C_{1-6}$  alkyl;

X is O or S;

$R_b$  and  $R_c$  are independently hydrogen or a halogen selected from Br, F, Cl or I; and

$R_e$  is  $-C_{1-6}$  alkyl or phenyl optionally substituted with  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, halogen, hydroxy, amino, mono( $C_{1-6}$ )alkylamino, di( $C_{1-6}$ )alkylamino, trifluoromethyl.

In another aspect, the invention provides compounds of formula Z51:



Z51

and pharmaceutically acceptable salts thereof wherein

m is 0-5;

B is aryl or heteroaryl optionally substituted with one or two groups independently selected from  $R_6$ ,  $R'_6$ ,  $R''_6$  and  $R'''_6$ , or

B is cycloalkyl or heterocycloalkyl optionally substituted with one, two, three, four, five, six, seven or eight groups independently selected from  $R_{6a}$ ,  $R_{6b}$ ,  $R'_{6a}$ ,  $R'_{6b}$ ,  $R''_{6a}$ ,  $R''_{6b}$ ,  $R'''_{6a}$  and  $R'''_{6b}$ ;

C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>7</sub> alkenyl or C<sub>2</sub>-C<sub>7</sub> alkynyl, each of which  
 is optionally substituted with one, two or three  
 groups selected from -NRR', -SR, -CN, -OCF<sub>3</sub>, -CF<sub>3</sub>, -  
 CONRR', -CO<sub>2</sub>R, -SO<sub>2</sub>NRR', -O-P(=O)(OR)(OR'), -N(R)-  
 5 C(=O)(R'), -N(R)(SO<sub>2</sub>R'), -SO<sub>2</sub>R, -C(=O)R, -NO<sub>2</sub>,  
 halogen, -(CH<sub>2</sub>)<sub>0-4</sub>-aryl, and -(CH<sub>2</sub>)<sub>0-4</sub>-heteroaryl, or  
 R and R' independently are -H, -(C<sub>1</sub>-C<sub>10</sub>) alkyl, -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>aryl</sub>,  
 -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>heteroaryl</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>heterocyclyl</sub>, or  
 C<sub>2</sub>-C<sub>7</sub> alkenyl or C<sub>2</sub>-C<sub>7</sub> alkynyl, each of which is optionally  
 10 substituted with one, two or three substituents  
 selected from the group consisting of halogen, -OH,  
 -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, mono- or  
 dialkylamino, and C<sub>1</sub>-C<sub>6</sub> alkyl, or  
 -(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with one,  
 15 two or three substituents selected from the group  
 consisting of halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub>  
 alkoxy, amino, mono- or dialkylamino, and C<sub>1</sub>-C<sub>6</sub>  
 alkyl;  
 benzyl where the phenyl ring is optionally substituted  
 20 with 1-3 groups independently selected from halogen,  
 -OH, -SH, -C≡N, mono or dialkylamino, C<sub>1</sub>-C<sub>6</sub> alkoxy,  
 or trifluoromethyl;  
 R<sub>6</sub>, R'<sub>6</sub>, R''<sub>6</sub>, R'''<sub>6</sub>, R<sub>6a</sub>, R<sub>6b</sub>, R'<sub>6a</sub>, R'<sub>6b</sub>, R''<sub>6a</sub>, R''<sub>6b</sub>, R'''<sub>6a</sub> and  
 R'''<sub>6b</sub> independently are -OR, -NO<sub>2</sub>, halogen, -CO<sub>2</sub>R, -C≡N, -  
 25 NRR', -SR, -SO<sub>2</sub>R, -C(=O)R, -OCF<sub>3</sub>, -CF<sub>3</sub>, -CONRR', -SO<sub>2</sub>NRR',  
 -O-P(=O)(OR)(OR'), -N(R)(COR'), -N(R)(SO<sub>2</sub>R'), -(CH<sub>2</sub>)<sub>0-4</sub>-CO-  
 NR<sub>7</sub>R'<sub>7</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-O-(CH<sub>2</sub>)<sub>0-4</sub>-CONRR', -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>1</sub>-C<sub>12</sub>  
 alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub> alkenyl), -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub>  
 alkynyl), -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>aryl</sub>, -  
 30 (CH<sub>2</sub>)<sub>0-4</sub>-R<sub>heteroaryl</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>heterocyclyl</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>aryl</sub>,  
 -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>heteroaryl</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>heterocyclyl</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-  
 R<sub>10</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-NR<sub>7</sub>R'<sub>7</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-SO-(C<sub>1</sub>-  
 C<sub>8</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>12</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>7</sub>



cycloalkyl),  $-(CH_2)_{0-4}-N(H \text{ or } R_{11})-CO-O-R_{11}$ ,  $-(CH_2)_{0-4}-N(H \text{ or } R_{11})-CO-N(R_{11})_2$ ,  $-(CH_2)_{0-4}-N(H \text{ or } R_{11})-CS-N(R_{11})_2$ ,  $-(CH_2)_{0-4}-N(H \text{ or } R_{11})-CO-R_7$ ,  $-(CH_2)_{0-4}-NR_7R'_7$ ,  $-(CH_2)_{0-4}-R_{10}$ ,  $-(CH_2)_{0-4}-O-CO-(C_1-C_6 \text{ alkyl})$ ,  $-(CH_2)_{0-4}-O-P(O)-(O-R_{aryl})_2$ ,  $-(CH_2)_{0-4}-O-CO-N(R_{11})_2$ ,  $-(CH_2)_{0-4}-O-CS-N(R_{11})_2$ ,  $-(CH_2)_{0-4}-O-(R_{11})$ ,  $-(CH_2)_{0-4}-O-(R_{11})-COOH$ ,  $-(CH_2)_{0-4}-S-(R_{11})$ ,  $C_3-C_7$  cycloalkyl,  $-(CH_2)_{0-4}-N(H \text{ or } R_{11})-SO_2-R_7$ , or  $-(CH_2)_{0-4}-C_3-C_7$  cycloalkyl, or  $C_1-C_8$  alkyl optionally substituted with one, two or three groups independently selected from  $C_1-C_6$  alkyl,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-OR$ ,  $-NO_2$ ,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CO_2R$ ,  $-C\equiv N$ ,  $-NRR'$ ,  $-SR$ ,  $-SO_2R$ ,  $-C(=O)R$ ,  $-OCF_3$ ,  $-CF_3$ ,  $-CONRR'$ ,  $-SO_2NRR'$ ,  $-O-P(=O)(OR)(OR')$ ,  $-N(R)(COR')$ ,  $-N(R)(SO_2R')$ ,  $-(CH_2)_{0-4}-CO-NR_7R'_7$ ,  $-(CH_2)_{0-4}-CO-(C_1-C_{12} \text{ alkyl})$ ,  $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkenyl})$ ,  $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkynyl})$ ,  $-(CH_2)_{0-4}-CO-(C_3-C_7 \text{ cycloalkyl})$ ,  $-(CH_2)_{0-4}-R_{aryl}$ ,  $-(CH_2)_{0-4}-R_{heteroaryl}$ ,  $-(CH_2)_{0-4}-R_{heterocyclyl}$ ,  $-(CH_2)_{0-4}-CO-R_{aryl}$ ,  $-(CH_2)_{0-4}-CO-R_{heteroaryl}$ ,  $-(CH_2)_{0-4}-CO-R_{heterocyclyl}$ ,  $-(CH_2)_{0-4}-CO-R_{10}$ ,  $-(CH_2)_{0-4}-CO-O-R_{11}$ ,  $-(CH_2)_{0-4}-SO_2-NR_7R'_7$ ,  $-(CH_2)_{0-4}-SO-(C_1-C_8 \text{ alkyl})$ ,  $-(CH_2)_{0-4}-SO_2-(C_1-C_{12} \text{ alkyl})$ ,  $-(CH_2)_{0-4}-SO_2-(C_3-C_7 \text{ cycloalkyl})$ ,  $-(CH_2)_{0-4}-N(H \text{ or } R_{11})-CO-O-R_{11}$ ,  $-(CH_2)_{0-4}-N(H \text{ or } R_{11})-CO-N(R_{11})_2$ ,  $-(CH_2)_{0-4}-N(H \text{ or } R_{11})-CS-N(R_{11})_2$ ,  $-(CH_2)_{0-4}-N(H \text{ or } R_{11})-CO-R_7$ ,  $-(CH_2)_{0-4}-NR_7R'_7$ ,  $-(CH_2)_{0-4}-R_{10}$ ,  $-(CH_2)_{0-4}-O-CO-(C_1-C_6 \text{ alkyl})$ ,  $-(CH_2)_{0-4}-O-P(O)-(O-R_{aryl})_2$ ,  $-(CH_2)_{0-4}-O-CO-N(R_{11})_2$ ,  $-(CH_2)_{0-4}-O-CS-N(R_{11})_2$ ,  $-(CH_2)_{0-4}-O-(R_{11})$ ,  $-(CH_2)_{0-4}-O-(R_{11})-COOH$ ,  $-(CH_2)_{0-4}-S-(R_{11})$ ,  $C_3-C_7$  cycloalkyl,  $-(CH_2)_{0-4}-N(H \text{ or } R_{11})-SO_2-R_7$ , or  $-(CH_2)_{0-4}-C_3-C_7$  cycloalkyl, or  $C_2-C_7$  alkenyl or  $C_2-C_7$  alkynyl, each of which is optionally substituted with one, two or three groups independently selected from halogen or  $-OH$ , or  $C_2-C_7$  alkenyl or  $C_2-C_7$  alkynyl, each of which is optionally substituted with one, two or three groups

independently selected from halogen, C<sub>1</sub>-C<sub>3</sub> alkyl, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino, or

5        -(CH<sub>2</sub>)<sub>0-4</sub>-O-(C<sub>1</sub>-C<sub>6</sub> alkyl), where the alkyl portion is optionally substituted with one, two, three, four, or five of halogen, or

any two of R<sub>6a</sub>, R<sub>6b</sub>, R'<sub>6a</sub>, R'<sub>6b</sub>, R''<sub>6a</sub>, R''<sub>6b</sub>, R'''<sub>6a</sub> and R'''<sub>6b</sub> together are oxo;

R<sub>7</sub> and R'<sub>7</sub> are the same or different and represent -H, -C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>2</sub> alkyl)-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl), -C<sub>2</sub>-C<sub>6</sub> alkenyl, -C<sub>2</sub>-C<sub>6</sub> alkynyl, -C<sub>1</sub>-C<sub>6</sub> alkyl chain with one double bond and one triple bond, or

10        -C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with -OH or -NH<sub>2</sub>; or;

15        -C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three groups independently selected from halogen; or heterocyclyl optionally substituted with halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, -SO<sub>2</sub>-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), -CO-NH<sub>2</sub>, -CO-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, oxo and -CO-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>; or

20        C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or

25        C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or

30        C<sub>1</sub>-C<sub>6</sub> alkoxy optionally substituted with one, two or three of halogen;

- aryl or heteroaryl, each of which is optionally substituted with halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, -SO<sub>2</sub>-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), -CO-NH<sub>2</sub>, -CO-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, and -CO-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>; or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or C<sub>1</sub>-C<sub>6</sub> alkoxy optionally substituted with one, two or three of halogen;
- R<sub>10</sub> is heterocyclyl optionally substituted with one, two, three or four groups independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl;
- R<sub>11</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>0-2</sub>-R<sub>aryl</sub>, or -(CH<sub>2</sub>)<sub>0-2</sub>-R<sub>heteroaryl</sub>;
- R<sub>aryl</sub> is aryl optionally substituted with halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, -SO<sub>2</sub>-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), -CO-NH<sub>2</sub>, -CO-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, or -CO-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>; or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or

C<sub>1</sub>-C<sub>6</sub> alkoxy optionally substituted with one, two or three of halogen;

R<sub>heteroaryl</sub> is heteroaryl, each of which is optionally substituted with halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, -SO<sub>2</sub>-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), -CO-NH<sub>2</sub>, -CO-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, or -CO-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>; or

C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or

C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or

C<sub>1</sub>-C<sub>6</sub> alkoxy optionally substituted with one, two or three of halogen;

R<sub>heterocyclyl</sub> is heterocyclyl optionally substituted with halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, -SO<sub>2</sub>-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), -CO-NH<sub>2</sub>, -CO-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, =O or -CO-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>; or

C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or

C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or

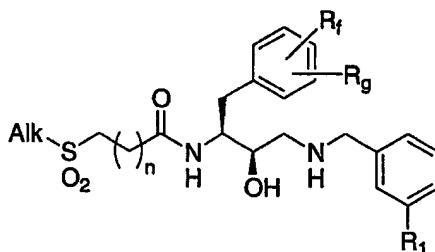
C<sub>1</sub>-C<sub>6</sub> alkoxy optionally substituted with one, two or three of halogen;

$R_2$  and  $R_3$  are independently hydrogen or  $C_1$ - $C_6$  alkyl; or

$R_2$  and  $R_3$  taken together with the carbon atom to which they are attached form a 3 or 4-membered ring;

$R_C$  is hydrogen or phenyl optionally substituted with  $C_1$ - $C_3$  alkyl,  $C_2$ - $C_4$  alkynyl, trifluoromethyl, or  $C_1$ - $C_2$  alkoxy.

In another aspect, the invention provides compounds of formula Z52:



10

Z52

or pharmaceutically acceptable salts thereof, wherein

$n$  is 0, 1, 2, or 3 (preferably 1);

$R_1$  is  $C_1$ - $C_3$  alkoxy (preferably methoxy), halogen (preferably iodo),  $C_1$ - $C_3$  alkyl (preferably ethyl or isopropyl), or  $C_2$ - $C_3$  alkynyl (preferably  $C_2$  alkynyl);

$R_f$  and  $R_g$  are independently halogen, or both are hydrogen; and Alk is  $C_1$ - $C_6$  alkyl (preferably methyl, ethyl, isobutyl or isopentyl).

Preferred examples of Z52 include those wherein  $n$  is 1 and  $R_1$  is methoxy,  $C_2$  alkynyl or ethyl. More preferably,  $R_1$  is methoxy.

The compounds of the invention inhibit beta-secretase and are therefor useful in treating and preventing Alzheimer's disease. The compounds of the invention are made by methods well known to those skilled in the art from starting compounds known to those skilled in the art. The process chemistry is well known to those skilled in the art. The most general process to prepare compounds of the invention is set forth in CHART A. Typically, amino acid (I) is protected at the amino

group, yielding protected amino acid (II). Compound (II) is converted to an ester intermediate, and the intermediate is reacted with a carbon nucleophile yielding compound (III). The ketone moiety in compound (III) is reduced to yield alcohol (IV), which forms epoxide(V). The addition of amine  $R_C-NH_2$  (VI) opens the epoxide, forming the protected alcohol (VII). The amine protecting group is removed, and the deprotected amine (VIII) is reacted with an amide forming agent of the formula  $(R_{N-1}-X_N)_2O$  or  $R_{N-1}-X_N-X_2$  or  $R_{N-1}-X_N-OH$  (IX) to produce a target compound of formula (X).

The backbone of the compounds of the invention is a hydroxyethylamine moiety,  $-NH-CH(R)-CH(OH)-$ . It can be readily prepared by methods disclosed in the literature and known to those skilled in the art. For example, *J. Med. Chem.*, 36, 288-291 (1992), *Tetrahedron Letters*, 28, 5569-5572 (1987), *J. Med. Chem.*, 38, 581-584 (1994) and *Tetrahedron Letters*, 38, 619-620 (1997) all disclose processes to prepare hydroxyethylamine type compounds.

CHART A sets forth a general method used in the invention to prepare the appropriately substituted amines (X). The compounds of the invention are prepared by starting with the corresponding amino acid (I). The amino acids (I) are well known to those skilled in the art or can be readily prepared from known compounds by methods well known to those skilled in the art. The substituted amines (X) of the invention have at least two enantiomeric centers which give four enantiomers. The first of these enantiomeric centers derives from the amino acid starting material (I). It is preferred to commercially obtain or produce the desired enantiomer (S) rather than produce an enantiomerically impure mixture and then have to separate out the desired enantiomer (S). It is preferred to start the process with enantiomerically pure (S)-amino acid (I)

of the same configuration as that of the substituted amine (X) product.

The first step of the process is to protect the free amino group of the (S)-amino acid (I) with an amino protecting group to produce the (S)-protected amino acid (II) by methods well known to those skilled in the art. Amino protecting groups are well known to those skilled in the art. See for example, "Protecting Groups in Organic Synthesis", John Wiley and sons, New York, N.Y., 1981, Chapter 7; "Protecting Groups in Organic Chemistry", Plenum Press, New York, N.Y., 1973, Chapter 2. The function of the amino protecting group is to protect the free amino functionality ( $-NH_2$ ) during subsequent reactions on the (S)-amino acid (I) which would not proceed well, either because the amino group would react and be functionalized in a way that is inconsistent with its need to be free for subsequent reactions, or the free amino group would interfere in the reaction. When the amino protecting group is no longer needed, it is removed by methods well known to those skilled in the art. By definition the amino protecting group must be readily removable as is known to those skilled in the art by methods well known to those skilled in the art. Suitable amino PROTECTING GROUP is selected from the group consisting of t-butoxycarbonyl, benzyloxycarbonyl, formyl, trityl, acetyl, trichloroacetyl, dichloroacetyl, chloroacetyl, trifluoroacetyl, difluoroacetyl, fluoroacetyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-ethoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(p-toluy)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl,

cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl, fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, 10 cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl and 1-piperidyloxycarbonyl, 9-fluorenylmethyl carbonate, -CH=CH=CH<sub>2</sub> and phenyl-C(=N)-H. It is preferred that the protecting group be *t*-butoxycarbonyl (BOC) and 15 benzyloxycarbonyl (CBZ), it is more preferred that the protecting group be *t*-butoxycarbonyl. One skilled in the art will understand the preferred methods of introducing a *t*-butoxycarbonyl or benzyloxycarbonyl protecting group and may additionally consult T.W. Green and P.G.M. Wuts in "Protective 20 Groups in Organic Chemistry," John Wiley and Sons, 1991 for guidance.

The (S)-protected compound (II) is transformed to a (S)-protected compound of formula (III) by first converting the (S)-protected amino acid (II) to a corresponding alkyl ester 25 according to methods well established in the art, for example by reaction with a diazocompound. The ester intermediate is then reacted with a carbanionic nucleophile of those known to those skilled in the art, for example an organometallic compound obtained by reacting a compound of formula X<sub>1</sub>-C(R<sub>2</sub>)(R<sub>3</sub>)-X<sub>1</sub> 30 with a strong metal base, wherein wherein the reaction yields a halogen-metal exchange, and wherein -X<sub>1</sub> is a halogen selected from the group consisting of chlorine, bromine or iodine. The addition of this carbanionic nucleophile to the ester intermediate yields the (S)-protected compound (III).



Suitable bases include, but are not limited to the alkylolithiums including, for example, *sec*-butyllithium, *n*-butyllithium, and *t*-butyllithium. Said reactions are preferably conducted at low temperature, for example -78 degrees C. Suitable reaction conditions include running the reaction in the presence of inert solvents or mixtures thereof, for example but not only ether, tetrahydrofuran or a mixture thereof. Wherein  $R_2$  and  $R_3$  are both hydrogen, then examples of  $X_1-C(R_2)(R_3)-X_1$  include dibromomethane, diiodomethane, chloriodomethane, bromiodomethane and bromochloromethane. One skilled in the art knows the preferred conditions required to conduct this reaction. Furthermore, if  $R_2$  and/or  $R_3$  are not -H, then by the addition of  $-C(R_2)(R_3)-X_1$  to esters of the (S)-protected amino acid (II) to produce the (S)-protected compound (III), an additional chiral center will be incorporated into the product, provided that  $R_2$  and  $R_3$  are not the same.

The (S)-protected compound (III) is then reduced by methods known to those skilled in the art for the reduction of ketones to the corresponding alcohol (IV). The reactants and reaction conditions for reducing the (S)-protected compound (III) to the corresponding alcohol (IV) include, for example, sodium borohydride, lithium borohydride, borane, diisobutylaluminum hydride, and lithium aluminium hydride. Sodium borohydride is the preferred reducing agent. The reduction is carried out for a period of time between 1 hour and 3 days at temperatures ranging from about -78 degrees C to the reflux temperature of the reaction mixture. It is preferred to conduct the reduction between about -78 degrees C and about 0 degrees C. A borane complex may be used, for example, borane-methyl sulfide complex, borane-piperidine complex, or borane-tetrahydrofuran complex. The preferred combination of reducing agents and reaction conditions needed are known to those skilled in the art, see for example, Larock, R.C. in Comprehensive Organic Transformations, VCH Publishers,

1989. The reduction of the (S)-protected compound (III) to the corresponding alcohol (IV) produces the second chiral center (third chiral center if  $R_2$  and  $R_3$  are not the same). The reduction of the (S)-protected compound (III) produces a  
5 mixture of enantiomers at the second center, (S, R/S)-alcohol (IV). This enantiomeric mixture is then separated by means known to those skilled in the art such as selective low-temperature recrystallization or chromatographic separation, for example by HPLC, employing commercially available chiral  
10 stationary phases. The enantiomer that is used in the remainder of the process of CHART A is the (S,S)-alcohol (IV) since this enantiomer is a precursor to the desired biologically active anti-Alzheimer (S,R)-substituted amine (X).

(S, S)-alcohol (IV) reacts intramolecularly to yield the  
15 corresponding epoxide (V) by means known to those skilled in the art. The stereochemistry of the ( carbon bound to the -OH moiety in compound (IV) is maintained in the epoxide (V). Preferred reaction conditions include contacting compound (IV) with a base, for example, but not limited to, sodium  
20 hydroxide, potassium hydroxide, or lithium hydroxide. Reaction conditions include the presence of a  $C_1$ - $C_6$  alcohol solvent; ethanol is preferred. A common co-solvent, for example ethyl acetate, may also be employed. The reactions is preferably conducted at temperatures ranging from about -45 degrees C to  
25 the reflux temperature of the reaction mixture; preferred temperature ranges are between about -20 degrees C and about 20-25 degrees C.

The epoxide (V) is then reacted with the appropriately substituted C-terminal amine,  $R_C-NH_2$  (VI) in reaction  
30 conditions known to those skilled in the art, leading to the opening the epoxide to yield the enantiomerically pure (S,R)-protected alcohol (VII). The substituted C-terminal amines,  $R_C-NH_2$  (VI) of this invention are commercially available or are known to those skilled in the art and can be readily prepared

from known compounds. Further, it is preferred that when R<sub>C</sub> is phenyl, it is substituted in the 3-position or 3,5-positions.

Suitable reaction conditions for opening the epoxide (V) include running the reaction in an organic, preferably inert w. C<sub>1</sub>-C<sub>6</sub> alcohol solvents are preferred and isopropyl alcohol most preferred. The reaction can be run at temperatures ranging from about 20-25 degrees C up to the reflux temperature of the reaction mixture and preferably at a temperature between about 50 degrees C and the reflux temperature of the reaction mixture. When the substituted C-terminal amine (VI) is a 1-amino-3,5-cis-dimethyl cyclohexyldicarboxylate it is preferably prepared as follows. To dimethyl-5-aminoisophthalate in acetic acid and methanol, is added rhodium in alumina in a high-pressure bottle. The bottle is saturated with hydrogen at 55 psi and shaken for one week of time. The mixture is then filtered through a layer of diatomaceous earth and rinsed with methanol three times, the solvents are removed under reduced pressure (with heat) to give a concentrate. The concentrate is triturated with ether and filtered again to give the desired C-terminal amine (VI). When the substituted C-terminal amine (VI) is 1-amino-3,5-cis-dimethoxy cyclohexane it is prepared by following the general procedure above and making non-critical variations but starting with 3,5-dimethoxyaniline. When the substituted C-terminal amine (VI) is an aminomethyl group where the substituent on the methyl group is an aryl group, for example NH<sub>2</sub>-CH<sub>2</sub>-R<sub>C</sub>-aryl, and NH<sub>2</sub>-CH<sub>2</sub>-R<sub>C</sub>-aryl is not commercially available it is preferably prepared as follows. A suitable starting material is the (appropriately substituted) aralkyl compound. The first step is bromination of the alkyl substituent via methods known to those skilled in the art, see for example R.C. Larock in Comprehensive Organic Transformations, VCH Publishers, 1989, p. 313. Next the alkyl halide is reacted with azide to produce the aryl-(alkyl)-azide. Last the azide is reduced to the corresponding amine by

hydrogen/catalyst to give the C-terminal amine (VI) of formula  $\text{NH}_2\text{-CH}_2\text{-R}_\text{C}\text{-aryl}$ . The suitably functionalized C-terminal amines (VI) may readily be prepared by one skilled in the art via known methods in the literature, making non-significant  
5 modifications. Select literature references include 1) Calderwood, et al., *Tet. Lett.*, 1997, 38, 1241, 2) Ciganek, J. *Org. Chem.*, 1992, 57, 4521, 3) Thurkauf, et al., *J. Med. Chem.*, 1990, 33, 1452, 4) Werner, et al., *Org. Syn., Coll. Vol. 5*, 273, 5) *J. Med. Chem.*, 1999, 42, 4193, 6) *Chem. Rev.* 1995, 95,  
10 2457, 7) *J. Am. Chem. Soc.*, 1986, 3150, 8) Felman et al., *J. Med. Chem.*, 1992, 35, 1183, 9) *J. Am. Chem. Soc.* 1970, 92, 3700, 10) *J. Med. Chem.*, 1997, 40, 2323.

CHART B discloses an alternative process for the synthesis of the enantiomerically pure (S,R)-protected alcohol (VII) from  
15 the (S)-protected compound (III). In this process, (S)-protected compound (III) is reacted with the appropriately substituted C-terminal amine  $\text{R}_\text{C}\text{-NH}_2$  (VI) in the preferred reaction conditions described above to yield (S)-protected ketone (XI) which is reduced in the preferred conditions  
20 described above to yield (S,R)-protected alcohol (VII).

CHART C discloses another alternative process for the synthesis of enantiomerically pure (S,R)-protected alcohol (VII) from the epoxide (V). Epoxide (V) is reacted with azide, yielding the enantiomerically pure (S,R)-protected azide (XII)  
25 in reaction conditions known to those skilled in the art, for example, J. March, *Advanced Organic Chemistry*, 3<sup>rd</sup> Edition, John Wiley & Sons Publishers, 1985, p. 380. (S,R)-protected azide (XII) is reduced to protected amine (XIII) by methods known to those skilled in the art for the reduction of an azide  
30 group in the presence of a *t*-butoxycarbonyl N-protecting group, for example catalytic hydrogenation. Alternative reducing conditions which may be used to avoid N-deprotection with protecting groups other than *t*-butoxycarbonyl are known to those skilled in the art, see for example, R.C. Larock in

Comprehensive Organic Transformations, VCH Publishers, 1989, p. 409.

The (S,R)-protected compound (XIII) is deprotected to yield (S,R)-amine (VII) by methods known to those skilled in the art for removal of amine protecting group. Suitable reaction conditions for the removal of an amine protecting group depend on the type of protecting group. For example, it is preferable to remove the preferred protecting group, BOC, by contacting (S,R)-protected alcohol (VII) with a mixture of and acid and an organic solvent, e.g. a trifluoroacetic acid/dichloromethane mixture, yielding the protonated salt of (S,R)-amine (VII). Optionally, (S,R)-amine (VII) can be purified by methods known to those skilled in the art, for example recrystallization. The free-base (S,R)-amine (VII) can be obtained by means known to those skilled in the art, such as for example, preparing the free base amine by contacting the salt with mild basic conditions. Additional BOC deprotection conditions and deprotection conditions for other protecting groups can be found in T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry," John Wiley and Sons, 1991, p. 309. Typical chemically suitable salts include trifluoroacetate, chloride, sulfate, phosphate; preferred is trifluoroacetate and chloride.

(S,R)-amine (VIII) is reacted with an appropriately substituted acylating reagent (IX) such as an anhydride, acyl halide, or acid of the formula  $(R_{N-1}-X_N)_2O$  or  $R_{N-1}-X_N-X_2$  or  $R_{N-1}-X_N-OH$  (IX) in reaction conditions known to those skilled in the art to produce (S,R)-substituted amine (X). Reaction conditions known to those skilled in the art can be found, for example, in R.C. Larock in Comprehensive Organic Transformations, VCH Publishers, 1989, p. 981, 979, and 972.  $R_N$  is preferably selected from the group consisting of:

$R_{N-1}-X_N$  wherein  $X_N$  is  $-CO-$ ,  $R_{N-1}$  is  $R_{N-aryl}$  or  $R_{N-heteroaryl}$  wherein  $R_{N-aryl}$  is phenyl where the substitution on phenyl is

1,3-, and wherein  $R_{N-ary1}$  or  $R_{N-heteroary1}$  are substituted with one -CO-NR<sub>N-2</sub>R<sub>N-3</sub>,

$R_{N-1}-X_N$ - wherein  $X_N$  is -CO-,  $R_{N-1}$  is  $R_{N-ary1}$  or  $R_{N-heteroary1}$  wherein  $R_{N-ary1}$  is phenyl substituted with one C<sub>1</sub> alkyl wherein  
 5 the substitution on the phenyl is 1,3,5-, and wherein  $R_{N-ary1}$  or  $R_{N-heteroary1}$  are substituted with one -CO-NR<sub>N-2</sub>R<sub>N-3</sub>,

$R_{N-1}-X_N$ - wherein  $X_N$  is -CO-, and  $R_{N-1}$  is  $R_{N-heteroary1}$  wherein  $R_{N-heteroary1}$  is substituted with one -CO-NR<sub>N-2</sub>R<sub>N-3</sub>.  $R_{N-2}$  and  $R_{N-3}$  are preferably the same and are C<sub>3</sub> alkyl,

10  $R_{N-1}-X_N$ - wherein  $X_N$  is -CO-, and  $R_{N-1}$  is  $R_{N-ary1}$  wherein  $R_{N-ary1}$  is phenyl substituted with one -CO-NR<sub>N-2</sub>R<sub>N-3</sub> wherein the substitution on phenyl is 1,3-,

$R_{N-1}-X_N$ - wherein  $X_N$  is -CO-, and  $R_{N-1}$  is  $R_{N-ary1}$  wherein  $R_{N-ary1}$  is phenyl substituted with one C<sub>1</sub> alkyl and with one -CO-NR<sub>N-2</sub>R<sub>N-3</sub>  
 15 3 wherein the substitution on the phenyl is 1,3,5-.  $X_N$  is preferably (A) -CO- and (B) -SO<sub>2</sub>-; more preferably  $X_N$  is -CO-.  $X_2$  is selected from the group consisting of -Cl, -Br; more preferably,  $X_2$  is -Cl.

Acylating reagents,  $(R_{N-1}-X_N)_2O$  or  $R_{N-1}-X_N-X_2$  or  $R_{N-1}-X_N-OH$  (IX) are known to those skilled in the art and are  
 20 commercially available or can be readily prepared from known starting materials by methods disclosed in the literature. Isophthalic acid derivatives (IX) of the formula  $R_{N-2}R_{N-3}N-CO$ -phenyl-CO- or methylisophthalic acid derivatives (IX) of the  
 25 formula

$R_{N-2}R_{N-3}N-CO-(CH_3-)$ phenyl-CO- where the substitution is 5-methyl-1,3-isophthalic acid are the preferred acylating reagents. The most preferred 5-methyl-1,3-isophthalic acid derivative is 3-[(N,N-dipropylamino)carbonyl]-5-methylbenzoic acid (IX). These  
 30 compounds are preferably synthesized according to the following method. An ester, preferably the monomethyl ester of isophthalic acid or methyl 5-methyl-1,3-isophthalate is dissolved in an organoanic solvent or a mixture of solvents, preferably a THF/DMF mixture. 1,1'-Carbonyldiimidazole is

added at a temperature of about 20-25 degrees C. A preferred amine ( $\text{H-NR}_{\text{N}-2}\text{R}_{\text{N}-3}$ ) is added. Following from about 1 hr to about 24 hrs of stirring at a temperature from about 20 degrees C to the reflux temperature of the reaction mixture, the reaction mixture is partitioned between saturated aqueous ammonium chloride and a water immiscible organic solvent, for example ethyl acetate. The aqueous layer is separated and extracted twice more with the organic solvent. The organic extracts are combined and washed with a saturated aqueous solutions of bicarbonate and saline and dried over anhydrous sodium sulfate or magnesium sulfate. Filtration of the drying agent and removal of solvents by reduced pressure yields the methyl ester of the desired  $\text{R}_{\text{N}-2}\text{R}_{\text{N}-3}\text{N-CO-phenyl-CO-O-CH}_3$  or a methylisophthalic acid acylating agent (IX)  $\text{R}_{\text{N}-2}\text{R}_{\text{N}-3}\text{N-CO-(CH}_3\text{-phenyl-CO-O-CH}_3$ . Purification of the (methyl) ester can be carried out for example via chromatography on silica gel eluting with a mixture of ethyl acetate and hexanes as mobile phase. The isophthalate ester or methylisophthalate ester of the mono-alkyl or di-alkyl amide is contacted with an aqueous alkaline solution, for example lithium hydroxide in a minimum amount of THF/methanol/water and stirred 3-24 hours at 20 degrees C to the reflux temperature of the reaction mixture. The solvents are then removed under reduced pressure and the products partitioned between water and a water immiscible solvent, for example ethyl acetate. If the formation of an emulsion hinders the separation of the two phases, a small amount of saline is added to aid the separation. The aqueous phase is extracted once more with a water immiscible solvent, for example ethyl acetate. The aqueous phase is then acidified via the addition of an acid, preferably hydrochloric acid, to  $\text{pH} \leq 3$ . The resulting mixture is extracted three times with a water immiscible solvent, for example ethyl acetate. The combined organic extracts are dried over anhydrous sodium or magnesium sulfate. The drying agent is removed by filtration

and the organic solvent is removed under reduced pressure to yield the product. The mono- or di-alkyl amide isophthalate/methylisophthalate is reacted with (S,R)-amine (VIII) to produce the (S,R)-substituted amine (X).

5        If  $R_{N-2}$  and  $R_{N-3}$  are both -H, the following method is preferred. An ester, preferably the methyl ester of isophthalate or methyl 5-methyl-1,3-isophthalate is dissolved in an organic solvent or a mixture of organic solvents, preferably a THF/DMF mixture. CDI is added at about 20-25  
10 degrees C. After five to thirty minutes, ammonia gas is bubbled into the mixture for 1 hr. The mixture is cooled to about 0 degrees C for the duration of the ammonia bubbling. The reaction mixture is left stirring under a balloon of ammonia overnight at about 20-25 degrees C, and partitioned between  
15 saturated aqueous ammonium chloride and a water immiscible solvent, for example ethyl acetate. The phases are separated and the aqueous phase is twice extracted with ethyl acetate. The organic extracts are washed with saturated aqueous solutions of bicarbonate and saline and dried over anhydrous  
20 sodium or magnesium sulfate. Filtration of the drying agent and removal of solvents under reduced pressure yields the ester of the desired isophthalic acid or the isophthalic acid derivative acylating reagent (IX). Purification of the (methyl) ester can be carried by example via chromatography on  
25 silica gel with an isopropanol/chloroform eluting mixture. The isophthalate ester or methylisophthalate ester of the primary amide is contacted with an aqueous alkaline solution such as lithium hydroxide in THF/methanol/water and stirred overnight at about 20-25 degrees C after which time the  
30 solvents are removed under reduced pressure and the solids are partitioned between water and a water immiscible solvent, for example ethyl acetate. If the formation of an emulsions hinders separation of the two phases, a small amount of saline solution is added to improve separation. The aqueous phase is



separated and extracted with a water immiscible solvent, for example ethyl acetate. The aqueous phase is then acidified with acid, preferably hydrochloric acid, to  $\text{pH} \leq 3$ . The resulting mixture is extracted with ethyl acetate. The combined organic extracts are dried over anhydrous sodium or magnesium sulfate. The drying agent is removed by filtration and the organic solvent removed under reduced pressure to yield the product. The amide isophthalic acid derivative is reacted with (VIII) to produce (X).

When it is preferred that the amine moiety be part of cyclic group, for example morpholinyl, piperazinyl, piperidinyl and pyrrolidinyl, etc the following method is preferably used. An ester, preferably the methyl ester of isophthalic acid or methyl 5-methyl-1,3-isophthalate is dissolved in an anhydrous solvent, for example methylene chloride, and a small quantity of a dipolar aprotic solvent, for example DMF is added. The mixture is cooled to about 0 degrees C and oxalyl chloride is added. The mixture is stirred at about 0 degrees C for about 30 minutes to about two hours after which the solvents are removed under reduced pressure. The crude acid chloride solid is left under vacuum overnight, and dissolved in dry methylene and cooled to about 0 degrees C prior to the addition of a cyclic amine and a tertiary amine base, for example N-methyl piperidine. The reaction mixture is stirred at about 0 degrees C for about 1 to about 6 hrs before the solvents are removed under reduced pressure. The residue is diluted with water and a water immiscible solvent, for example ethyl acetate, for example, and the phases are separated. The aqueous phase is extracted with a water immiscible solvent, for example ethyl acetate, , and the combined organic extracts are washed with saturated aqueous bicarbonate and dried over anhydrous sodium or magnesium sulfate. Filtration of the drying agent and removal of solvents under reduced pressure yields the product cyclic

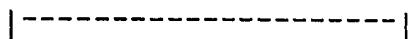
amide. The cyclic amide is contacted with an aqueous alkaline solution, for example lithium hydroxide in THF/methanol/water and stirred overnight at about 20-25 degrees C, after which time the solvents are removed under reduced pressure and the  
5 residue is partitioned between water and a water immiscible solvent, for example ethyl acetate. The aqueous phase is extracted with ethyl acetate. Removal of water from the aqueous phase under reduced pressure yields the target cyclic amide product (IX).

10 When the  $R_{N-1}$  moiety in the target product is a carbocycle, for example but not limited to, cyclohexane, with the starting reagent may be a suitably functionalized dimethyl isophthalate and the method one of those taught in the literature (Meyers, A.I., *Org. Syn.*, 1971, 51, 103) one may  
15 reduce the six-membered ring with reducing agents such as rhodium (5%) on alumina in the presence of acetic acid and methanol under a hydrogen atmosphere to afford the corresponding dimethyl cyclohexane dicarboxylate.

CHART D sets forth an alternative process for production  
20 of the (S,R)-substituted amine (X) from the (S,R)-protected azide (XII), which is produced from the corresponding epoxide (V) in CHART C. The amino protecting group is removed to produce the corresponding unprotected azide (XIV) by methods previously described in CHART A for the conversion of (S,R)-  
25 protected alcohol (VII) to the corresponding (S,R)-amine (VIII). The (S,R)-unprotected azide (XIV) is then acylated on nitrogen to produce the corresponding (S,R)-azide (XV). Next, the azide functionality is reduced as previously discussed for the conversion of the (S,R)-protected azide (XII) to the  
30 corresponding (S,R)-protected amine (XIII) to give the (S,R)-free amine (XVI). Last, the (S,R)-free amine (XVI) is transformed to the corresponding (S,R)-substituted amine (X) by nitrogen alkylation with a compound of the formula  $R_C-X_3$  to give the corresponding (S,R)-substituted amine (X).  $X_3$  is an

appropriate leaving group, such as but not limited to, -Cl, -Br, -I, -O-mesylate, -O-tosylate, O-triflate, etc.  $X_3$  may also be an aldehyde; the corresponding coupling with (XVI) via the well known reductive amination procedure gives the (S,R)-  
 5 substituted amine (X).

Carbocyclic amide forming agents (IX) are also provided for by the invention. For example, the carbocyclic amide forming agents of the formula



10  $R'-CH-C(R'')(R''')-CH-X_N-OH$  (IX) are readily prepared from known starting materials by methods disclosed in the literature and known to those skilled in the art, for example, *J. Med. Chem.* **1998**, *41*, 1581, *J. Org. Chem.* **2000**, *65*, 1305. It is also understood that instead of the carboxylic acid, one may readily  
 15 employ an acyl halide, where the halide is preferably chloride, or a suitable group to produce a mixed anhydride; these methods are taught by CHART A. For additional guidance on the formation of carbocycles and preferably cyclopropanes, one may consult M.P. Doyle; M.A. McKerverly; T. Ye in *Modern Catalytic*  
 20 *Methods for Organic Synthesis with Diazo Compounds From Cyclopropanes to Ylides*, Wiley-Interscience, **1998**, pp. 163-279.

CHARTs E, F, G, and H disclose various methods to produce the  $R_N$  portion of the substituted amine (X) where the phenyl ring of the  $R_N$  1,3-disubstituted moiety,  
 25 -CO-phenyl-CO-, is further substituted in the 5-position with various groups such as amides, nitriles, halides, and amines. These compounds are prepared by methods known to those skilled in the art. The process chemistry of each reaction is known to those skilled in the art. The novelty here is represented by  
 30 the order of each process step and/or the specific reactants used. One skilled in the art knowing the desired product would know at least one method to prepare the desired product by using known starting materials. Hence, the following

discussion is not necessary but is set forth to further aid those interested in preparing the compounds of the invention.

CHART E discloses alternate processes for the transformation of the aniline (XVII) or acid ester (XVIII) to the corresponding acid (IX-XXIII). One process begins with the commercially available aniline (XVII). The aniline (XVII) is treated with a diazotizing reagent such as sodium or potassium nitrite in mineral acid, followed by a halogen source such as copper (II) halide or alkali metal halide, or by an organic diazotizing reagent such as an alkyl nitrite in a strong acid such as acetic acid or trifluoroacetic acid, followed by a halide source such as copper (II) halide or alkali metal halide to give the halo acid ester (XIX).

Alternatively, the acid ester (XVIII) is treated with N-halosuccinimide and trifluoromethanesulfonic acid to give the halo acid ester (XIX). The halo acid ester (XIX) is then converted to the ester amide (XXI) using a primary or secondary amine of the formula  $H-NG_1G_2$  where  $G_1$  and  $G_2$  are the same or different or can be cyclized.  $G_1$  and  $G_2$  become part of the substituted amine (X) and are included in the definition of  $R_N$ .  $R_N$  includes  $R_{N-1}-X_N-$  where the linker,  $-X_N-$ , includes  $-CO-$  and  $R_{N-1}$  includes  $R_{N-aryl}$ .  $R_{N-aryl}$  is defined to include phenyl (-phenyl) optionally substituted with one or two amides:

- CO-NR<sub>N-2</sub>R<sub>N-3</sub> and
- CO-R<sub>N-4</sub>.

Alternatively, the halo acid ester (XIX) is converted to the acid chloride halo ester (XX) by methods known to those skilled in the art. One of skill in the art will appreciate that other acid halides may also be used. The dihalo ester (XX) is treated with a primary or secondary amine of the formula  $H-NG_1G_2$  to give the ester amide (XXI). The ester amide (XXI) is then reacted with an AMINE in a carbon monoxide atmosphere in the presence of a palladium catalyst using methods such as those reviewed by Heck, (Palladium Reagents in

Organic Synthesis, 1985 pp. 342-365). to give the diamide (XXII). Hydrolysis of the ester portion of the diamide (XXII) using methods well known to those skilled in the art gives the diamide acid (XXIII).

5 In CHART F, an alternate route to intermediate diamide (XXII) is shown starting from commercially available phenol (XXIV). The phenol (XXIV) is treated with a trifluoromethanesulfonating reagent such as trifluoromethanesulfonic anhydride to give triflate (XXV). The  
10 triflate (XXV) is reacted under the conditions of palladium catalysis in the presence of carbon monoxide and an amine of the formula  $H-NR_{N\alpha}R_{N\beta}$  (AMINE) as for the conversion of the ester amide (XXI) to the corresponding diamide (XXII) in CHART E to give the diester (XXVI). The diester (XXVI) is hydrolyzed  
15 using methods known to those skilled in the art to give the monoacid (XXVII). The monoacid (XXVII) is then converted to the diamide (XXII) using conditions such as for the conversion of the halo acid ester (XIX) to the ester amide (XXI) in CHART E.

20 CHART G discloses another route to prepare the ester amide (XXI). The reaction starts with commercially available nitro compound (XXVIII) which is condensed with an (AMINE) using coupling methods known to those skilled in the art to give the nitro amide (XXX). The nitro amide (XXX) can also be prepared  
25 by first treating the nitro compound (XXVIII) with reagents such as thionyl chloride, or DMF and oxalyl chloride, or other methods known to those skilled in the art to give the acyl chloride (XXIX), which upon treatment with the (AMINE) gives the nitro amide (XXX). Reduction of the nitro amide (XXX)  
30 using methods known to those skilled in the art (see, for example, Smith and March, Advanced Organic Chemistry, 5<sup>th</sup> ed.) gives amide aniline (XXXI). The amide aniline (XXXI) is then treated with diazotizing reagents such as sodium or potassium nitrite in mineral acid, followed by a halogen source such as

copper (II) halide or alkali metal halide, or by an organic diazotizing reagent such as an alkyl nitrite in a strong acid such as acetic acid or trifluoroacetic acid, followed by a halide source such as copper (II) halide or alkali metal halide  
5 to give the ester amide (XXI).

CHART H discloses a process to prepare the diamide acid (IX-XXIII) from the ester amide (XXI), where one of the amides is unsubstituted and is  $-CO-NH_2$ . This process starts from either the ester or the acid, for example the ester amide (XXI)  
10 is treated with copper (I) cyanide (CuCN) in N-methylpyrrolidinone or DMF, preferably N-methylpyrrolidinone, to give the nitrile (XXXII). The nitrile (XXXII) is converted to the primary amide (XXXIII) using urea-hydrogen peroxide complex (see *Synth. Commun.* (1993) 3149) or the methods of  
15 *Synth. Commun.* (1990) 1445, *Synth. Commun.* (1997) 3119, *J. Org. Chem.* (1992) 2521, *Tet. Lett.* (1996) 6555, *Ind. J. Chem., Sect. B*, (1999) 974, *Tet. Lett.* (1995) 3469, *Tet. Lett.* (1998) 3005, or others. When the ester amide (XXI) is in the form of an ester, an additional hydrolysis step using lithium hydroxide,  
20 sodium hydroxide, potassium hydroxide, barium hydroxide, or other hydrolysis methods known to those skilled in the art is used to convert the diamide ester (XXXIII) to the diamide acid (IX-XXIII).

CHART I discloses an alternate synthetic route from the  
25 protected alcohol (VII) to the substituted amine (X) which uses a diprotected intermediate (XXXIV) wherein the nitrogen atom attached to the  $R_c$  substituent is protected. Using the process of CHART I, the mono protected alcohol (VII) is reacted with a new protecting group to form the orthogonally protected  
30 (XXXIV). This is a common strategy employed in traditional peptide chemistry by those skilled in the art, see M. Bodansky, *Principles of Peptide Chemistry*. When the mono protected alcohol (VII) is protected with CBZ one skilled in the art could react it with either  $(BOC)_2O$  in methylene chloride or

similar organic solvent or FMOC-Cl in methylene chloride or similar organic solvent to prepare orthogonally protected (XXXIV). Then the CBZ group is removed by hydrogenation in the presence of a catalytic amount of palladium on carbon in an alcoholic solvent, such as methanol, or ethyl acetate, or with catalytic palladium on carbon in alcoholic solvents in the presence of ammonium formate as is known to those skilled in the art. This gives the  $R_C$ -N protected (XXXV). Similarly, when the mono protected alcohol (VII) is protected as a BOC it can be reacted with CBZ-Cl under Schotten-Bauman conditions or CBZ-OSu in THF to prepare the reversed (XXXIV). Then the BOC group can be cleaved with hydrochloric acid (4 N) in methanol, ethanol or dioxane or with trifluoroacetic acid in methylene chloride or by other methods such as those described in The Peptides, Analysis, Synthesis, Biology, Vol. 3, Ed. E. Gross and J. Meienhofer (1981) to liberate the CBZ  $R_C$ -N protected (XXXV). This functional group manipulation gives various permutations in the sequence (VII) to (XXXIV) to (XXXV) as is apparent to one skilled in the art. When the appropriately  $R_C$ -N protected compound (XXXV) is reacted with the amide forming agent (IX), in acid form, under standard peptide coupling conditions, for example, EDC/HOBt in methylene chloride or DMF or a previously activated acid,  $(R_N)_2O$  gives the corresponding  $R_N$ -substituted  $R_C$ -N protected (XXXVI). Simple de-protection of the  $R_N$ -substituted  $R_C$ -N protected (XXXVI) then gives the desired substituted amine (X). Thus when the  $R_N$ -substituted  $R_C$ -N protected (XXXVI) is protected with BOC, treatment with hydrochloric acid (4N) in dioxane or the other reagents discussed above gives the substituted amine (X). When the  $R_N$ -substituted  $R_C$ -N protected (XXXVI) is protected with CBZ, treatment with hydrogen from 10 - 50 psi in alcoholic solvents, such as methanol with a catalytic amount of palladium on carbon will give, after work-up, the desired substituted amine (X). Similarly when the  $R_N$ -substituted  $R_C$ -N protected (XXXVI) is

protected with Fmoc, treatment with a secondary amine, preferably either piperidine (10 %) or diethylamine (10 %) in an inert solvent such as, for example, methylene chloride will give after work up the desired substituted amine (X).

5 CHART J discloses a process to prepare compounds where the phenyl ring of the  $R_N$  substituent of  $-CO-phenyl-CO-$  is substituted with a sulfonamide group in the 5-position. The process starts with the halo amide ester (XXI, CHART E) which is reacted with sodium nitrite, sulfur dioxide, copper chloride  
10 (II) and acetic acid by the method disclosed in *J. Med. Chem.*, 42, 3797 (1999) to prepare the sulfonyl chloride (XXXVII). The sulfonyl chloride (XXXVII) is then reacted with AMINE, as defined above, by methods known to those skilled in the art to produce the corresponding sulfonamide (XXXVIII). Last the  
15 sulfonamide (XXXVIII) is transformed to the corresponding sulfonamide acid (XXXIX) by methods known to those skilled in the art such as using lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, or other hydrolysis methods known to those skilled in the art.

20 CHART K discloses how to prepare the  $R_N$  substituents where  $R_N$  is  $R_{N-1}-X_N-$ , where  $X_N$  is  $-CO-$  and  $R_{N-1}$  is  $R_{N-aryl}$  where  $R_{N-aryl}$  is phenyl substituted with one alkyl group and one  $-CO-NR_{N-2}R_{N-3}$  or  $-CO-R_{N-4}$ . See the discussion above for CHART E regarding the amine,  $H-NR_{N\alpha}R_{N\beta}$  (AMINE), used to form the amide  $R_N$   
25 substituents. The process starts with the halo amide ester (XXI) which is then reacted with an alkyl boronic acid having the desired alkyl group in the presence of a palladium catalyst such as  $Pd(PPh_3)Cl_2$  using the general method described in *J. Med. Chem.*, 4288 (2000). The alkyl boronic acids are  
30 commercially available or can be prepared by the process described in *J. Am. Chem. Soc.*, 60, 105 (1938). It is preferred that  $R_{N-b}$  is bromo. This step produces the alkyl ester (XL) which is then hydrolyzed by means known to those skilled in the art to produce the desired alkyl acid (XLI).



CHART L discloses a process to prepare the amide forming agent (IX - XLVII) where the  $R_N$  substituent is  $R_{N-1}-X_N-$ , where the linker,  $-X_N-$  is  $-CO-$ , where  $R_{N-1}$  is  $R_{N-aryl}$  and where  $R_{N-aryl}$  is phenyl (-phenyl) substituted with groups:

- 5  $C_1-C_6$  alkyl, optionally substituted with one, two or three substituents selected from the group consisting of  $C_1-C_3$  alkyl,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-OH$ ,  $-SH$ ,  $-C\equiv N$ ,  $-CF_3$ ,  $C_1-C_3$  alkoxy,  $-NR_{1-a}R_{1-b}$  where  $R_{1-a}$  and  $R_{1-b}$  are as defined above, and  $-N(-H$  and  $C_1-C_3$  alkyl) $-CO-R_{N-5}$ . This specific amide forming agent, (IX - XLVII)
- 10 is prepared by starting with the phenyl nitro compound (XLII) which is reduced to the corresponding phenyl nitro hydroxy compound (XLIII) using borane-methyl sulfide or borane in THF. The phenyl nitro hydroxy compound (XLIII) is reduced to the corresponding phenyl amino hydroxy compound (XLIV) using
- 15 hydrogen and palladium catalyst as is known to those skilled in the art. The phenyl amino hydroxy compound (XLIV) is reacted with an aldehyde in the presence of a reducing agent such as sodium cyanoborohydride or sodium triacetoxyborohydride to give the phenyl substituted amino hydroxy compound (XLV). The
- 20 phenyl substituted amino hydroxy compound (XLV) is acylated with an acid chloride or acid anhydride by methods known to those skilled in the art to give the phenyl disubstituted amino hydroxy compound (XLVI). The phenyl disubstituted amino hydroxy compound (XLVI) is hydrolyzed using an alkali
- 25 hydroxide, followed by acidification, to give the amide forming agent (IX - XLVII). The amide forming agent (XLVII) is then coupled with amine (VIII) using methods known to those skilled in the art and methods previously discussed, such as with diethyl cyanophosphonate, to give the substituted amine (X).
- 30 Further treatment of the substituted amine (X) with diethyl cyanophosphonate gives the substituted amine where the hydroxyalkyl substituent on the phenyl ring has a phosphate substituent.

CHART M discloses a process to prepare amide forming agents (IX- L) where the  $R_N$  substituent is  $R_{N-1}-X_N-$ , where the linker,  $-X_N-$  is  $-CO-$ , where  $R_{N-1}$  is  $R_{N-aryl}$  and where  $R_{N-aryl}$  is phenyl (-phenyl) substituted with two groups. The first  
 5 substituent at what is usually identified as position "5-" can be either:

$-R_{N-aryl}$  or

$-R_{N-heteroaryl}$ . The second substituent at what is usually identified as position "3-" can be either:

10  $-CO-NR_{N-2}R_{N-3}$  or

$-CO-R_{N-4}$ .  $R_{N\alpha}$  and  $R_{N\beta}$  include both the non-cyclic amides,  $-CO-NR_{N-2}R_{N-3}$  and the cyclic amides  $-CO-R_{N-4}$  where  $R_{N-2}$ ,  $R_{N-3}$  and  $R_{N-4}$  are as defined in the claims. The process starts with the trisubstituted phenyl compound (XLVIII) where  $R_{N-d}$  is  $-Cl$ ,  $-Br$ ,  $-I$  or  $-O$ -triflate. Treatment with  
 15 an aryl or heteroaryl boronic acid or heteroaryl or aryl boronic acid ester such as (aryl or heteroaryl)- $B(OH)_2$  or (aryl or heteroaryl)- $B(OR^a)(OR^b)$  (where  $R^a$  and  $R^b$  are lower alkyl, ie.  $C_1-C_6$ , or taken together,  $R^a$  and  $R^b$  are  
 20 lower alkylene, ie.  $C_2-C_{12}$ ) in the presence of a metal catalyst with or without a base in an inert solvent yields (XLIX). Metal catalysts in these transformations include, but are not limited to, salts or phosphine complexes of Cu, Pd, or Ni (eg.  $Cu(OAc)_2$ ,  $PdCl_2(PPh_3)_2$ ,  $NiCl_2(PPh_3)_2$ ).  
 25 Bases may include, but are not limited to, alkaline earth metal carbonates, alkaline earth metal bicarbonates, alkaline earth metal hydroxides, alkali metal carbonates, alkali metal bicarbonates, alkali metal hydroxides, alkali metal hydrides (preferably sodium hydride), alkali metal  
 30 alkoxides (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium

bis(trimethylsilyl)amide), trialkyl amines (preferably diisopropylethylamine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, acetonitrile, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylacetamides (preferably dimethylacetamide), N,N-dialkylformamides (preferably dimethylformamide), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes (preferably methylene chloride). Preferred reaction temperatures range from room temperature up to the boiling point of the solvent employed. The reactions may be run in conventional glassware or in one of many commercially available parallel synthesizer units. Non-commercially available boronic acids or boronic acid esters may be obtained from the corresponding optionally substituted aryl halide as described in *Tetrahedron*, 50, 979-988 (1994). Intermediate (XLIX) is then hydrolyzed using alkali metal hydroxide, for example lithium, sodium or potassium hydroxide, followed by acidification, to give aryl or heteroaryl coupled acids (IX-L). Alternatively, as described in *Tetrahedron*, 50, 979-988 (1994), one may convert the  $R_N-d$  to the corresponding boronic acid or boronic acid ester  $(OH)_2B-$  or  $(OR^a)(OR^b)B-$  and obtain the same products set forth above by treating with a suitable aryl or heteroaryl halide or triflate.

CHART N discloses a process to prepare amide forming agents (IX - LII) where the  $R_N$  substituent is  $R_{N-1}-X_N-$  where the linker,  $-X_N-$  is  $-CO-$ , where  $R_{N-1}$  is  $R_{N-aryl}$  and where  $R_{N-aryl}$  is phenyl (-phenyl) substituted with two groups. The first substituent at what is usually identified as position "5-" is  $-C\equiv C-R$ . The second substituent at what is usually identified as

postion "3-" can be either  $-\text{CO}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$  or  $-\text{CO}-\text{R}_{\text{N}-4}$ . The halo ester (XXI) is treated with a mixture of  $\text{PdCl}_2(\text{Pphenyl}_3)_2$  and trimethylsilyl acetylene, using methods known to those skilled in the art, to give acetylene ester (LI). Acetylene ester (LI) is then hydrolyzed using alkali metal hydroxide, followed by acidification, to give acetylene acid (IX - LII).

CHARTS O and O' disclose processes to prepare amide forming agents (IX - LX) and (IX - LXIII) with an extended methylene group where the  $\text{R}_{\text{N}}$  substituent is  $\text{R}_{\text{N}-1}-\text{X}_{\text{N}}-$  where the linker,  $-\text{X}_{\text{N}}-$  is  $-\text{CO}-$ , where  $\text{R}_{\text{N}-1}$  is  $\text{R}_{\text{N-aryl}}$  and where  $\text{R}_{\text{N-aryl}}$  is phenyl ( $-\text{phenyl}$ ) substituted with two groups. The substituent at what is usually identified as postion "3-" can be either  $-\text{CO}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$  or  $-\text{CO}-\text{R}_{\text{N}-4}$ . In the process of CHART O, the substituent at the 5-position is  $-\text{CH}_2\text{CO}-\text{NH}_2$  and in the process of CHART O', the substituent at the 5-position is  $-\text{CH}_2\text{C}\equiv\text{N}$ . The starting diester acid (LIII) is reduced with borane in solvents such as THF to give the corresponding diester alcohol (LIV). The diester alcohol (LIV) is converted to the corresponding diester bromo compound (LV) using a brominating agent such as  $\text{PBr}_3$ ,  $\text{CBr}_4$ , or other halogenating agent such as are known to those skilled in the art. The bromine of the diester bromo compound (LV) is then displaced with cyanide to give the corresponding nitrile (LVI). In CHART O', the nitrile (LVI) is then hydrolyzed to the corresponding cyano ester (LXI). The cyano ester (LXI) is then coupled with  $\text{H}-\text{NR}_{\text{Na}}\text{R}_{\text{Nb}}$  (AMINE), as previously described using methods known to those skilled in the art to give the corresponding cyano amide (LXII). The cyano amide (LXII) is then hydrolyzed to the corresponding cyano acid (IX-LXIII) which is in turn coupled with amine (VIII) to give the substituted amine (X). When the substituent on the extended methyl group is  $-\text{CO}-\text{NH}_2$ , the process of CHART O is used. There the nitrile (LVI) is converted to the corresponding diester amine (LVII) by methods known to those skilled in the art. The next steps are the same

as for CHART O' where the diester amide (LVII) is hydrolyzed to the corresponding ester amine (LVIII) which is then converted to the corresponding diamide ester (LIX) which is hydrolyzed to the corresponding diamide acid (IX - LX). The diamide acid (IX - XL) is then coupled with the appropriate amine (VIII) to produce the desired substituted amide (X).

CHART P discloses a process to prepare amide forming agents (IX - LXVII) with an extended hydroxymethylene group where the  $R_N$  substituent is  $R_{N-1}-X_N-$  where the linker,  $-X_N-$  is -CO-, where the  $R_{N-1}$  is  $R_{N-aryl}$ , where  $R_{N-aryl}$  is phenyl (-phenyl) substituted with two groups. The substituent at what is usually identified as position "3-" can be either  $-CO-NR_{N-2}R_{N-3}$  or  $-CO-R_{N-4}$ . The process begins with a halo amide (LXIV), preferably iodo, which is converted to the corresponding aldehyde (LXV) and then to the corresponding alcohol (LXVI) by the method described in *Synth. Commun.* 28, 4270 (1998), optionally with variations known to those skilled in the art. Hydrolysis of the alcohol (LXVI) using alkali hydroxides, followed by acidification, gives the desired hydroxy acid (IX - LXVII). The hydroxy acid (IX - LXVII) is then coupled with the appropriate amine (VIII) to give the desired substituted amine (X).

CHART Q discloses a process to prepare amide forming agents (IX - LXXII) with an alkyl group or a halogen atom or an amino group at the 5-position where the  $R_N$  substituent is  $R_{N-1}-X_N-$  where the linker,  $-X_N-$  is -CO-, where the  $R_{N-1}$  is  $R_{N-aryl}$ , where  $R_{N-aryl}$  is phenyl (-phenyl) substituted with two groups. The substituent at what is usually identified as position "3-" can be either  $-CO-NR_{N-2}R_{N-3}$  or  $-CO-R_{N-4}$ . The process begins with an appropriately 5-substituted diacid (LXVIII) which is esterified by methods known to those skilled in the art to give the corresponding diester (LXIX). The diester (LXIX) is then hydrolyzed using alkali hydroxides, followed by acidification, to give the corresponding monoacid (LXX). Alternatively, the

monoacid (LXX) can be produced directly from the diacid (LXVIII) by known methods. The monoacid (LXX) is then coupled with  $H-NR_{\alpha}R_{\beta}$  (AMINE)

to give the corresponding amide ester (LXXI). The amide ester (LXXI) is then hydrolyzed using alkali hydroxides, followed by acidification, to give the corresponding acid amide (IX - LXXII).

CHART R discloses a general process to prepare the amide forming agents (IX - LXXVII) which, for example, have an alkyl group at what is known as the 5-position and a ketone at the 3-position. These acids (IX- LXXVII) are formed by starting with the acid (LXXIII) which is converted to the corresponding acid halide (LXXIV) using methods known to those skilled in the art. The acid halide (LXXIV) is preferably the acid chloride. The acid halide (LXXIV) in the presence of copper (I) bromide and tetrahydrofuran and at temperatures ranging from -78 degrees C to 0 degreesC is treated with a Grignard reagent (aryl-Mg-X, or alkyl-Mg-X, where X is -Cl or -Br) to give the ketone esters (LXXVI and LXXVI'). Many Grignard reagents are available for purchase; others are prepared by methods known to those skilled in the art. An alternative method for preparing the ketone esters (LXXVI, LXXVI') is to prepare the Weinreb amide (LXXV), either from the acid (LXXIII) directly or by way of acid halide (LXXIV) followed by treatment with N,O-dimethylhydroxylamine to give Weinreb amide (LXXV) and then treating the Weinreb amide (LXXV) with a Grignard reagent, by methods known to those skilled in the art. The ketone esters (LXXVI, LXXVI') are then hydrolyzed using alkali hydroxides, followed by acidification, to give the ketone acids (LXXVII, LXXVII').

CHART S discloses various methods to modify the  $R_N$  portion of the substituted amine (X) where the phenyl ring of the  $R_N$  moiety is further substituted in the 3-position with various groups such as aryl and heteroaryl. These compounds are

prepared by methods known to those skilled in the art. The process chemistry of each reaction is known to those skilled in the art. What is novel here is the order of each process step and/or the specific reactants used. One skilled in the art knowing the desired product would know at least one method to prepare the desired product by using known starting materials. Hence, the following discussion is not necessary but is set forth to further aid those interested in preparing the compounds of the invention.

10 CHART S sets forth a general method used in the invention to prepare the substituted amines (X) where  $R_N = R_N\text{-aryl-}R_N\text{-aryl-X}_N$  or  $R_N\text{-heteroaryl-}R_N\text{-aryl-X}_N$ . Treatment of the (S,R)-amine (VIII) with amide forming agents (IX) according to the methods set forth above where for CHART S,  $R_{N-1}$  is Br- $R_N\text{-aryl}$  generates the corresponding (S,R)-substituted amine (X) where  $R_N$  is Br- $R_N\text{-aryl-X}_N$ . Further treatment with an aryl boronic acid or aryl boronic acid ester such as (aryl or heteroaryl)-B(OH)<sub>2</sub> or (aryl or heteroaryl)-B(OR<sup>a</sup>)(OR<sup>b</sup>) (where R<sup>a</sup> and R<sup>b</sup> are lower alkyl, ie. C<sub>1</sub>-C<sub>6</sub>, or taken together, R<sup>a</sup> and R<sup>b</sup> are lower alkylene, ie. C<sub>2</sub>-C<sub>12</sub>) in the presence of a metal catalyst with or without a base in an inert solvent yields the (S,R)-substituted amine (X) where  $R_N$  is  $R_N\text{-aryl-}R_N\text{-aryl-X}_N$  or  $R_N\text{-heteroaryl-}R_N\text{-aryl-X}_N$ . Metal catalysts in these transformations include, but are not limited to, salts or phosphine complexes of Cu, Pd, or Ni (eg. Cu(OAc)<sub>2</sub>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>). Bases may include, but are not limited to, alkaline earth metal carbonates, alkaline earth metal bicarbonates, alkaline earth metal hydroxides, alkali metal carbonates, alkali metal bicarbonates, alkali metal hydroxides, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal

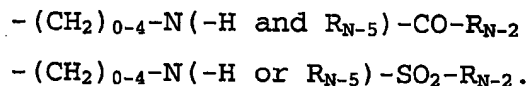
dialkylamides (preferably lithium diisopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably diisopropylethylamine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, acetonitrile, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylacetamides (preferably dimethylacetamide), N,N-dialkylformamides (preferably dimethylformamide), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes (preferably methylene chloride). Preferred reaction temperatures range from room temperature up to the boiling point of the solvent employed. The reactions may be run in conventional glassware or in one of many commercially available parallel synthesizer units. Non-commercially available boronic acids or boronic acid esters may be obtained from the corresponding optionally substituted aryl halide as described in *Tetrahedron*, 50, 979-988 (1994).

Where the above chemistry is incompatible with other functionality in the (S,R)-substituted amine (X) where  $R_N$  is  $Br-NR-aryl-X_N$ , then one skilled in the art will readily understand that an alternative sequence of coupling steps is required. For example, treatment of an appropriately substituted amide forming agent (IX)  $R_{N-1}-X_N-OH$  where  $R_{N-1}$  is  $Br-R_N-aryl$  with a boronic acid or boronic acid ester under the conditions described above will afford the appropriately substituted amide forming agent (IX) where  $R_{N-1}$  is  $NR-aryl-NR-aryl$  or  $R_N-heteroaryl-R_N-aryl$ . When the amide forming agent (IX) where  $R_{N-1}$  is  $NR-aryl-NR-aryl$  or  $R_N-heteroaryl-R_N-aryl$  is treated with the (S,R)-amine (VIII), one then obtains the same substituted amines (X) set forth in CHART S.



The above examples for CHART S are not meant to limit the scope of the chemistry. In addition to bromine, a suitable group may include iodine or triflate. Alternatively, as described in *Tetrahedron*, 50, 979-988 (1994), one may convert  
 5 the Br-R<sub>N</sub>-aryl to the corresponding boronic acid or boronic acid ester (OH)<sub>2</sub>B-R<sub>N</sub>-aryl or (OR<sup>a</sup>)(OR<sup>b</sup>)B-R<sub>N</sub>-aryl and obtain the same products set forth above by treating with a suitable aryl or heteroaryl halide or triflate. Additionally, each -R<sub>N</sub>-aryl and -R<sub>N</sub>-heteroaryl are interchangeable at each occurrence in  
 10 the chemistry described above.

CHART T discloses a process to prepare amide forming agents (IX - LXXIX) where the R<sub>N</sub> substituent is R<sub>N-1</sub>-X<sub>N</sub>-, where the linker, -X<sub>N</sub>- is -CO-, where R<sub>N-1</sub> is R<sub>N</sub>-aryl and where R<sub>N</sub>-aryl is phenyl substituted with -CO-NR<sub>Nalpha</sub>R<sub>Nbeta</sub> (AMINE) and with an  
 15 amide of the formulas:



The process begins with the amide aniline (XXXI) which is reacted with the corresponding acid halide or sulfonyl halide,  
 20 or acid anhydride or sulfonyl anhydride to produce the corresponding amide ester (LXXVIII). Suitable solvents include THF or dichloromethane at temperatures ranging from -78 degrees to 100 degrees C. The amide ester (LXXVIII) is then hydrolyzed to the corresponding amide acid (IX - LXXIX) by methods known  
 25 to those skilled in the art. When the amide forming agent (IX - LXXIX) is reacted with the appropriate amine (VIII), the desired compound (X) is obtained.

CHART U discloses a general method for preparing various C-terminal amines (VI) as recited by the preparation of  
 30 C-terminal amine (LXXXIV). Methods to prepare amines of this type are well understood using methods known to those skilled in the art, or one may consult the references: 1) *JACS*, 1970, 92, 3700, and 2) US patent 4,351,842.

CHART V further discloses general methods for preparing various C-terminal amines (VI) as recited by the preparation of C-terminal amines (LXXXIX). Multiple examples of the heterocyclic carboxylic acids or acid chlorides are commercially available. Optionally, the carboxylic acid (LXXXV) may be converted to the acid chloride (LXXXVI) with reagents such as, but not limited to, thionyl chloride. Displacement with ammonia generates the common intermediate amides (LXXXVII) which are readily reduced to amines (VI - LXXXIX) using a variety of methods detailed previously. Alternatively, other heteroaryls are commercially available as the methyl halide (LXXXVIII) which are treated with ammonia to yield the title C-terminal amines (VI - LXXXVIII).

CHART W discloses general methods for preparing thiazolyl containing C-terminal amines as recited by the preparation of C-terminal amines (LXXXXI). The synthesis of the thiazoles is outlined in CHART W; these procedures are amply taught in the literature and are modified from the procedures outlined in: Mashraqui, SH; Keehn, PM. *J. Am. Chem. Soc.* 1982, 104, 4461-4465. The synthesis of substituted 5-aminomethylthiazoles (XCI) was achieved from 5-hydroxymethylthiazole (XC) by the procedure described in: Alterman et al. *J. Med. Chem.* 1998, 41, 3782-3792. All other thiazole analogs were transformed to the hydroxymethyl derivative using CHART W, and converted to the aminomethyl derivative by the Alterman procedure without notable changes.

CHART X discloses general methods for preparing isoxazolyl containing C-terminal amines as recited by the preparation of C-terminal amines (XCII). The synthesis of isoxazole derivatives was modified from the procedure in: Felman, SW et al. *J. Med. Chem.* 1992, 35, 1183-1190 and is readily understood by those skilled in the art making non-notable changes to achieve the

title compounds. The substituted hydroxylamine precursors were synthesized using the procedure taught by Bousquet, EW. *Org. Synth. Coll. Vol II*, 313-315. Commercially available propargylamine may be protected using any number of methods known in the art (see: Greene, TW; Wuts, PGM. *Protective Groups in Organic Synthesis*, 3<sup>rd</sup> Ed. New York: John Wiley, 1999. Chapter 7.), preferred is a BOC protecting group. Substituted propargyl amines may be obtained by a number of methods commonly known in the art.

10 CHART Y discloses a general route to prepare hydroxyethylamines where one carbon atom of the peptide backbone, along with R<sub>2</sub> and R<sub>3</sub> form a ring. It is understood that the invention also allows for a heteroatom to be incorporated into the ring. In summary, the synthesis of  
15 compounds where R<sub>2</sub> and R<sub>3</sub> may form a ring proceeds from a suitably protected amino acid aldehyde and cycloalkyllithium species, both of which are commercially available or where known procedures for making such compounds are known in the art. The general procedure involved is also precedent in the  
20 literature, for example, see Klumpp, et al., *J. Am. Chem. Soc.*, 1979, 101, 7065, and it is intended that making non-critical variations, one may obtain the title compounds provided for by CHART Y. Treatment of a suitably protected amino acid aldehyde and cycloalkyllithium species affords alcohol (XCIII). These  
25 reactions are carried out in an inert solvent such as, for example, tetrahydrofuran or diethyl ether. Optimally the reactions are conducted at low temperatures, for example below 0 degrees C. Carbonylation via the Klumpp procedure yields the acid (XCIV) which when exposed to Curtius, or related  
30 procedures well known to those skilled in the art, generates the primary amine (XCV). The primary amines (XCV) may be capped C-terminally via the conditions set forth in CHART C & D followed by nitrogen deprotection and capping N-terminally via the conditions set forth in CHART A.

The compounds of the invention may contain geometric or optical isomers as well as tautomers. Thus, the invention includes all tautomers and pure geometric isomers, such as the *E* and *Z* geometric isomers, as well as mixtures thereof.

5 Furthermore, the invention includes pure enantiomers and diastereomers as well as mixtures thereof, including racemic mixtures. The individual geometric isomers, enantiomers, or diastereomers may be prepared or isolated by methods known in the art.

10 Compounds of the invention with the stereochemistry designated in formula X may be included in mixtures, including racemic mixtures, with other enantiomers, diastereomers, geometric isomers or tautomers. Compounds of the invention with the stereochemistry designated in formula X are typically  
15 in these mixtures in excess of 50 percent. Preferably, compounds of the invention with the stereochemistry designated in formula X are in these mixtures in excess of 80 percent. Most preferably, compounds of the invention with the stereochemistry designated in formula X are in these mixtures  
20 in excess of 90 percent.

The compounds of the invention are typically amines and as such form salts when reacted with acids. Pharmaceutically acceptable salts are preferred over the corresponding (S,R)-substituted amines (X) and the substituted amines with R<sub>N</sub>  
25 cyclized (X') since they produce compounds which are more water soluble, stable and/or more crystalline. Pharmaceutically acceptable salts are any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered  
30 and in the context in which it is administered. Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The preferred pharmaceutically acceptable salts include salts of the following acids: acetic, aspartic, benzenesulfonic, benzoic, bicarbonic, bisulfuric, bitartaric,

butyric, calcium edetate, camsylic, carbonic, chlorobenzoic, citric, edetic, edisylic, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycollylarsanilic, hexamic, hexylresorcinoic, hydrabamic, hydrobromic, 5 hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, maleic, malic, malonic, mandelic, methanesulfonic, methylnitric, methylsulfuric, mucic, muconic, napsylic, nitric, oxalic, p-nitromethanesulfonic, pamoic, pantothenic, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, 10 phthalic, polygalactouronic, propionic, salicylic, stearic, succinic, succinic, sulfamic, sulfanilic, sulfonic, sulfuric, tannic, tartaric, teoclic and toluenesulfonic. For other acceptable salts, see *Int. J. Pharm.*, 33, 201-217 (1986) and *J. Pharm. Sci.*, 66(1), 1, (1977).

15 The invention provides compounds, compositions, kits, and methods for inhibiting beta-secretase enzyme activity and A beta peptide production. Inhibition of beta-secretase enzyme activity halts or reduces the production of A beta from APP and reduces or eliminates the formation of beta-amyloid deposits in 20 the brain.

#### Methods of the Invention

The compounds of the invention, and pharmaceutically acceptable salts thereof, are useful for treating humans or 25 animals suffering from a condition characterized by a pathological form of beta-amyloid peptide, such as beta-amyloid plaques, and for helping to prevent or delay the onset of such a condition. The compounds and compositions of the invention are particularly useful for treating or preventing Alzheimer's 30 disease. The compounds of the invention can either be used individually or in combination, as is best for the patient.

As used herein, the term "treating" means that the compounds of the invention can be used in humans with at least a tentative diagnosis of disease. The compounds of the

invention will delay or slow the progression of the disease thereby giving the individual a more useful life span.

The term "preventing" means that the compounds of the invention are useful when administered to a patient who has not  
5 been diagnosed as possibly having the disease at the time of administration, but who would normally be expected to develop the disease or be at increased risk for the disease. The compounds of the invention will slow the development of disease symptoms, delay the onset of the disease, or prevent the  
10 individual from developing the disease at all. Preventing also includes administration of the compounds of the invention to those individuals thought to be predisposed to the disease due to age, familial history, genetic or chromosomal abnormalities, and/or due to the presence of one or more biological markers  
15 for the disease, such as a known genetic mutation of APP or APP cleavage products in brain tissues or fluids.

In treating or preventing the above diseases, the compounds of the invention are administered in a therapeutically effective amount. The therapeutically  
20 effective amount will vary depending on the particular compound used and the route of administration, as is known to those skilled in the art.

In addition, the compounds of the invention can also be used with inhibitors of P-glycoprotein (P-gp). The use of P-gp  
25 inhibitors is known to those skilled in the art. See for example, *Cancer Research*, 53, 4595-4602 (1993), *Clin. Cancer Res.*, 2, 7-12 (1996), *Cancer Research*, 56, 4171-4179 (1996), International Publications WO99/64001 and WO01/10387. The important thing is that the blood level of the P-gp inhibitor  
30 be such that it exerts its effect in inhibiting P-gp from decreasing brain blood levels of the compounds of the invention. To that end the P-gp inhibitor and the compounds of the invention can be administered at the same time, by the same or different route of administration, or at different times.

The important thing is not the time of administration but having an effective blood level of the P-gp inhibitor.

Suitable P-gp inhibitors include cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, VX-710, LY335979, PSC-833, GF-102,918 and other steroids. It is to be understood that additional agents will be found that do the same function and are also considered to be useful.

10 The P-gp inhibitors can be administered orally, parenterally, (IV, IM, IM-depo, SQ, SQ-depo), topically, sublingually, rectally, intranasally, intrathecally and by implant.

The therapeutically effective amount of the P-gp inhibitors is from about 0.1 to about 300 mg/kg/day, preferably about 0.1 to about 150 mg/kg daily. It is understood that while a patient may be started on one dose, that dose may have to be varied over time as the patient's condition changes.

When administered orally, the P-gp inhibitors can be administered in usual dosage forms for oral administration as is known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so that the P-gp inhibitors need to be administered only once or twice daily. The oral dosage forms are administered to the patient one thru four times daily. It is preferred that the P-gp inhibitors be administered either three or fewer times a day, more preferably once or twice daily. Hence, it is preferred that the P-gp inhibitors be administered in solid dosage form and further it is preferred that the solid dosage form be a sustained release form which permits once or twice daily dosing. It is preferred that what ever dosage form is

used, that it be designed so as to protect the P-gp inhibitors from the acidic environment of the stomach. Enteric coated tablets are well known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also well known to those skilled in the art.

In addition, the P-gp inhibitors can be administered parenterally. When administered parenterally they can be administered IV, IM, depo-IM, SQ or depo-SQ.

10 The P-gp inhibitors can be given sublingually. When given sublingually, the P-gp inhibitors should be given one thru four times daily in the same amount as for IM administration.

The P-gp inhibitors can be given intranasally. When given by this route of administration, the appropriate dosage forms are a nasal spray or dry powder as is known to those skilled in the art. The dosage of the P-gp inhibitors for intranasal administration is the same as for IM administration.

20 The P-gp inhibitors can be given intrathecally. When given by this route of administration the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art.

The P-gp inhibitors can be given topically. When given by this route of administration, the appropriate dosage form is a cream, ointment or patch. Because of the amount of the P-gp inhibitors needed to be administered the patch is preferred. However, the amount that can be delivered by a patch is limited. Therefore, two or more patches may be required. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the P-gp inhibitors be delivered as is known to those skilled in the art.

The P-gp inhibitors can be administered rectally by suppository as is known to those skilled in the art.



The P-gp inhibitors can be administered by implants as is known to those skilled in the art.

There is nothing novel about the route of administration nor the dosage forms for administering the P-gp inhibitors.

5 Given a particular P-gp inhibitor, and a desired dosage form, one skilled in the art would know how to prepare the appropriate dosage form for the P-gp inhibitor.

It should be apparent to one skilled in the art that the exact dosage and frequency of administration will depend on the

10 particular compounds of the invention administered, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is well known to those skilled in

15 the art.

#### **Dosage forms and amounts**

The compounds of the invention can be administered orally, parenternally, (IV, IM, depo-IM, SQ, and depo SQ),

20 sublingually, intranasally (inhalation), intrathecally, topically, or rectally. Dosage forms known to those of skill in the art are suitable for delivery of the compounds of the invention.

Compositions are provided that contain therapeutically

25 effective amounts of the compounds of the invention. The compounds are preferably formulated into suitable pharmaceutical preparations such as tablets, capsules, or elixirs for oral administration or in sterile solutions or suspensions for parenteral administration. Typically the

30 compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art.

About 1 to 500 mg of a compound or mixture of compounds of the invention or a physiologically acceptable salt or ester is

compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in those compositions or preparations is such that a suitable dosage in the range indicated is obtained. The compositions are preferably formulated in a unit dosage form, each dosage containing from about 2 to about 100 mg, more preferably about 10 to about 30 mg of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

To prepare compositions, one or more compounds of the invention are mixed with a suitable pharmaceutically acceptable carrier. Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion, or the like. Liposomal suspensions may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for lessening or ameliorating at least one symptom of the disease, disorder, or condition treated and may be empirically determined.

Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, or have another action. The

compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients.

Where the compounds exhibit insufficient solubility, methods for solubilizing may be used. Such methods are known and include, but are not limited to, using cosolvents such as dimethylsulfoxide (DMSO), using surfactants such as Tween®, and dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as salts or prodrugs may also be used in formulating effective pharmaceutical compositions.

The concentration of the compound is effective for delivery of an amount upon administration that lessens or ameliorates at least one symptom of the disorder for which the compound is administered. Typically, the compositions are formulated for single dosage administration.

The compounds of the invention may be prepared with carriers that protect them against rapid elimination from the body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, microencapsulated delivery systems. The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in known *in vitro* and *in vivo* model systems for the treated disorder.

The compounds and compositions of the invention can be enclosed in multiple or single dose containers. The enclosed compounds and compositions can be provided in kits, for example, including component parts that can be assembled for use. For example, a compound inhibitor in lyophilized form and a suitable diluent may be provided as separated components for combination prior to use. A kit may include a compound inhibitor and a second therapeutic agent for co-administration.

The inhibitor and second therapeutic agent may be provided as separate component parts. A kit may include a plurality of containers, each container holding one or more unit dose of the compound of the invention. The containers are preferably adapted for the desired mode of administration, including, but not limited to tablets, gel capsules, sustained-release capsules, and the like for oral administration; depot products, pre-filled syringes, ampules, vials, and the like for parenteral administration; and patches, medipads, creams, and the like for topical administration.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the active compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

If oral administration is desired, the compound should be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its

integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

Oral compositions will generally include an inert diluent  
5 or an edible carrier and may be compressed into tablets or enclosed in gelatin capsules. For the purpose of oral therapeutic administration, the active compound or compounds can be incorporated with excipients and used in the form of tablets, capsules, or troches. Pharmaceutically compatible  
10 binding agents and adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches, and the like can contain any of the following ingredients or compounds of a similar nature: a binder such as, but not limited to, gum  
15 tragacanth, acacia, corn starch, or gelatin; an excipient such as microcrystalline cellulose, starch, or lactose; a disintegrating agent such as, but not limited to, alginic acid and corn starch; a lubricant such as, but not limited to, magnesium stearate; a gildant, such as, but not limited to,  
20 colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and a flavoring agent such as peppermint, methyl salicylate, or fruit flavoring.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such  
25 as a fatty oil. In addition, dosage unit forms can contain various other materials, which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the  
30 like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings, and flavors.

The active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action.

Solutions or suspensions used for parenteral, 5 intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent such as water for injection, saline solution, fixed oil, a naturally occurring vegetable oil such as sesame oil, coconut oil, peanut oil, cottonseed oil, and the like, or a synthetic fatty vehicle 10 such as ethyl oleate, and the like, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antimicrobial agents such as benzyl alcohol and methyl parabens; antioxidants such as ascorbic acid and sodium bisulfite; chelating agents such as ethylenediaminetetraacetic 15 acid (EDTA); buffers such as acetates, citrates, and phosphates; and agents for the adjustment of tonicity such as sodium chloride and dextrose. Parenteral preparations can be enclosed in ampoules, disposable syringes, or multiple dose vials made of glass, plastic, or other suitable material. 20 Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Where administered intravenously, suitable carriers include physiological saline, phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents 25 such as glucose, polyethylene glycol, polypropyleneglycol, and mixtures thereof. Liposomal suspensions including tissue-targeted liposomes may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known for example, as described in U.S. Patent No. 30 4,522,811.

The active compounds may be prepared with carriers that protect the compound against rapid elimination from the body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but not

limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid, and the like. Methods for  
5 preparation of such formulations are known to those skilled in the art.

The compounds of the invention can be administered orally, parenternally (IV, IM, depo-IM, SQ, and depo-SQ), sublingually, intranasally (inhalation), intrathecally, topically, or  
10 rectally. Dosage forms known to those skilled in the art are suitable for delivery of the compounds of the invention.

Compounds of the invention may be administered enterally or parenterally. When administered orally, compounds of the invention can be administered in usual dosage forms for oral  
15 administration as is well known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions, and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained  
20 release type so that the compounds of the invention need to be administered only once or twice daily.

The oral dosage forms are administered to the patient 1, 2, 3, or 4 times daily. It is preferred that the compounds of the invention be administered either three or fewer times, more  
25 preferably once or twice daily. Hence, it is preferred that the compounds of the invention be administered in oral dosage form. It is preferred that whatever oral dosage form is used, that it be designed so as to protect the compounds of the invention from the acidic environment of the stomach. Enteric  
30 coated tablets are well known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also well known to those skilled in the art.

When administered orally, an administered amount therapeutically effective to inhibit beta-secretase activity, to inhibit A beta production, to inhibit A beta deposition, or to treat or prevent AD is from about 0.1 mg/day to about 1,000 mg/day. It is preferred that the oral dosage is from about 1 mg/day to about 100 mg/day. It is more preferred that the oral dosage is from about 5 mg/day to about 50 mg/day. It is understood that while a patient may be started at one dose, that dose may be varied over time as the patient's condition changes.

Compounds of the invention may also be advantageously delivered in a nano crystal dispersion formulation. Preparation of such formulations is described, for example, in U.S. Patent 5,145,684. Nano crystalline dispersions of HIV protease inhibitors and their method of use are described in US 6,045,829. The nano crystalline formulations typically afford greater bioavailability of drug compounds.

The compounds of the invention can be administered parenterally, for example, by IV, IM, depo-IM, SC, or depo-SC. When administered parenterally, a therapeutically effective amount of about 0.5 to about 100 mg/day, preferably from about 5 to about 50 mg daily should be delivered. When a depot formulation is used for injection once a month or once every two weeks, the dose should be about 0.5 mg/day to about 50 mg/day, or a monthly dose of from about 15 mg to about 1,500 mg. In part because of the forgetfulness of the patients with Alzheimer's disease, it is preferred that the parenteral dosage form be a depo formulation.

The compounds of the invention can be administered sublingually. When given sublingually, the compounds of the invention should be given one to four times daily in the amounts described above for IM administration.

The compounds of the invention can be administered intranasally. When given by this route, the appropriate dosage



forms are a nasal spray or dry powder, as is known to those skilled in the art. The dosage of the compounds of the invention for intranasal administration is the amount described above for IM administration.

5       The compounds of the invention can be administered intrathecally. When given by this route the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art. The dosage of the compounds of the invention for intrathecal administration is the amount  
10       described above for IM administration.

      The compounds of the invention can be administered topically. When given by this route, the appropriate dosage form is a cream, ointment, or patch. Because of the amount of the compounds of the invention to be administered, the patch is  
15       preferred. When administered topically, the dosage is from about 0.5 mg/day to about 200 mg/day. Because the amount that can be delivered by a patch is limited, two or more patches may be used. The number and size of the patch is not important, what is important is that a therapeutically effective amount of  
20       the compounds of the invention be delivered as is known to those skilled in the art. The compounds of the invention can be administered rectally by suppository as is known to those skilled in the art. When administered by suppository, the therapeutically effective amount is from about 0.5 mg to about  
25       500 mg.

      The compounds of the invention can be administered by implants as is known to those skilled in the art. When administering a compound of the invention by implant, the therapeutically effective amount is the amount described above  
30       for depot administration.

      The invention here is the new compounds of the invention and new methods of using the compounds of the invention. Given a particular compound of the invention and a desired dosage

form, one skilled in the art would know how to prepare and administer the appropriate dosage form.

The compounds of the invention are used in the same manner, by the same routes of administration, using the same pharmaceutical dosage forms, and at the same dosing schedule as described above, for preventing disease or treating patients with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating or preventing Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, Frontotemporal dementias with parkinsonism (FTDP) and diffuse Lewy body type of Alzheimer's disease.

The compounds of the invention can be used in combination, with each other or with other therapeutic agents or approaches used to treat or prevent the conditions listed above. Such agents or approaches include: acetylcholine esterase inhibitors such as tacrine (tetrahydroaminoacridine, marketed as COGNEX®), donepezil hydrochloride, (marketed as Aricept® and rivastigmine (marketed as Exelon®); gamma-secretase inhibitors; anti-inflammatory agents such as cyclooxygenase II inhibitors; anti-oxidants such as Vitamin E and ginkgolides; immunological approaches, such as, for example, immunization with A beta peptide or administration of anti-A beta peptide antibodies; statins; and direct or indirect neurotropic agents such as Cerebrolysin®, AIT-082 (Emilieu, 2000, Arch. Neurol. 57:454), and other neurotropic agents of the future.

It should be apparent to one skilled in the art that the exact dosage and frequency of administration will depend on the particular compounds of the invention administered, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, and other medication the individual may be taking as is well known to administering physicians who are skilled in this art.

#### 10 **Inhibition of APP Cleavage**

The compounds of the invention inhibit cleavage of APP between Met595 and Asp596 numbered for the APP695 isoform, or a mutant thereof, or at a corresponding site of a different isoform, such as APP751 or APP770, or a mutant thereof (sometimes referred to as the "beta secretase site"). Inhibitory activity is demonstrated in one of a variety of inhibition assays, whereby cleavage of an APP substrate in the presence of a beta-secretase enzyme is analyzed in the presence of the inhibitory compound, under conditions normally sufficient to result in cleavage at the beta-secretase cleavage site. Reduction of APP cleavage at the beta-secretase cleavage site compared with an untreated or inactive control is correlated with inhibitory activity. Assay systems that can be used to demonstrate efficacy of the compound inhibitors of the invention are known. Reative assay systems are described, for example, in U.S. Patents No. 5,942,400, 5,744,346, as well as in the Examples below.

The enzymatic activity of beta-secretase and the production of A beta can be analyzed *in vitro* or *in vivo*, using natural, mutated, and/or synthetic APP substrates, natural, mutated, and/or synthetic enzyme, and the test compound. The analysis may involve primary or secondary cells expressing native, mutant, and/or synthetic APP and enzyme, animal models expressing native APP and enzyme, or may utilize transgenic

animal models expressing the substrate and enzyme. Detection of enzymatic activity can be by analysis of one or more of the cleavage products, for example, by immunoassay, flurometric or chromogenic assay, HPLC, or other means of detection.

- 5 Inhibitory compounds are determined as those having the ability to decrease the amount of beta-secretase cleavage product produced in comparison to a control, where beta-secretase mediated cleavage in the reaction system is observed and measured in the absence of inhibitory compounds.

10

#### **Beta-secretase**

- Various forms of beta-secretase enzyme are known, and are available and useful for assay of enzyme activity and inhibition of enzyme activity. These include native,  
15 recombinant, and synthetic forms of the enzyme. Human beta-secretase is known as Beta Site APP Cleaving Enzyme (BACE), Asp2, and memapsin 2, and has been characterized, for example, in U.S. Patent No. 5,744,346 and published PCT patent applications WO98/22597, WO00/03819, WO01/23533, and  
20 WO00/17369, as well as in literature publications (Hussain et.al., 1999, *Mol.Cell.Neurosci.* 14:419-427; Vassar et.al., 1999, *Science* 286:735-741; Yan et.al., 1999, *Nature* 402:533-537; Sinha et.al., 1999, *Nature* 40:537-540; and Lin et.al., 2000, *PNAS USA* 97:1456-1460). Synthetic forms of the enzyme  
25 have also been described (WO98/22597 and WO00/17369). Beta-secretase can be extracted and purified from human brain tissue and can be produced in cells, for example mammalian cells expressing recombinant enzyme.

- Useful inhibitory compounds are effective to inhibit 50%  
30 of beta-secretase enzymatic activity at a concentration of less than 50 micromolar, preferably at a concentration of 10 micromolar or less, more preferably 1 micromolar or less, and most preferably 10 nanomolar or less.

**APP substrate**

Assays that demonstrate inhibition of beta-secretase-mediated cleavage of APP can utilize any of the known forms of APP, including the 695 amino acid "normal" isotype described by Kang et.al., 1987, *Nature* 325:733-6, the 770 amino acid isotype described by Kitaguchi et. al., 1981, *Nature* 331:530-532, and variants such as the Swedish Mutation (KM670-1NL) (APP-SW), the London Mutation (V7176F), and others. See, for example, U.S. Patent No. 5,766,846 and also Hardy, 1992, *Nature Genet.* 1:233-234, for a review of known variant mutations. Additional useful substrates include the dibasic amino acid modification, APP-KK disclosed, for example, in WO 00/17369, fragments of APP, and synthetic peptides containing the beta-secretase cleavage site, wild type (WT) or mutated form, e.g., SW, as described, for example, in U.S. Patent No 5,942,400 and WO00/03819.

The APP substrate contains the beta-secretase cleavage site of APP (KM-DA or NL-DA) for example, a complete APP peptide or variant, an APP fragment, a recombinant or synthetic APP, or a fusion peptide. Preferably, the fusion peptide includes the beta-secretase cleavage site fused to a peptide having a moiety useful for enzymatic assay, for example, having isolation and/or detection properties. A useful moiety may be an antigenic epitope for antibody binding, a label or other detection moiety, a binding substrate, and the like.

**Antibodies**

Products characteristic of APP cleavage can be measured by immunoassay using various antibodies, as described, for example, in Pirttila et.al., 1999, *Neuro.Lett.* 249:21-4, and in U.S. Patent No. 5,612,486. Useful antibodies to detect A beta include, for example, the monoclonal antibody 6E10 (Senetek, St. Louis, MO) that specifically recognizes an epitope on amino acids 1-16 of the A beta peptide; antibodies 162 and 164 (New

York State Institute for Basic Research, Staten Island, NY) that are specific for human A beta 1-40 and 1-42, respectively; and antibodies that recognize the junction region of beta-amyloid peptide, the site between residues 16 and 17, as described in U.S. Patent No. 5,593,846. Antibodies raised against a synthetic peptide of residues 591 to 596 of APP and SW192 antibody raised against 590-596 of the Swedish mutation are also useful in immunoassay of APP and its cleavage products, as described in U.S. Patent Nos. 5,604,102 and 5,721,130.

### **Assay Systems**

Assays for determining APP cleavage at the beta-secretase cleavage site are well known in the art. Exemplary assays, are described, for example, in U.S. Patent Nos. 5,744,346 and 5,942,400, and described in the Examples below.

### **Cell free assays**

Exemplary assays that can be used to demonstrate the inhibitory activity of the compounds of the invention are described, for example, in WO00/17369, WO 00/03819, and U.S. Patents No. 5,942,400 and 5,744,346. Such assays can be performed in cell-free incubations or in cellular incubations using cells expressing a beta-secretase and an APP substrate having a beta-secretase cleavage site.

An APP substrate containing the beta-secretase cleavage site of APP, for example, a complete APP or variant, an APP fragment, or a recombinant or synthetic APP substrate containing the amino acid sequence: KM-DA or NL-DA, is incubated in the presence of beta-secretase enzyme, a fragment thereof, or a synthetic or recombinant polypeptide variant having beta-secretase activity and effective to cleave the beta-secretase cleavage site of APP, under incubation conditions suitable for the cleavage activity of the enzyme.

Suitable substrates optionally include derivatives that may be fusion proteins or peptides that contain the substrate peptide and a modification useful to facilitate the purification or detection of the peptide or its beta-secretase cleavage products. Useful modifications include the insertion of a known antigenic epitope for antibody binding; the linking of a label or detectable moiety, the linking of a binding substrate, and the like.

Suitable incubation conditions for a cell-free *in vitro* assay include, for example: approximately 200 nanomolar to 10 micromolar substrate, approximately 10 to 200 picomolar enzyme, and approximately 0.1 nanomolar to 10 micromolar inhibitor compound, in aqueous solution, at an approximate pH of 4 -7, at approximately 37 degrees C, for a time period of approximately 10 minutes to 3 hours. These incubation conditions are exemplary only, and can be varied as required for the particular assay components and/or desired measurement system. Optimization of the incubation conditions for the particular assay components should account for the specific beta-secretase enzyme used and its pH optimum, any additional enzymes and/or markers that might be used in the assay, and the like. Such optimization is routine and will not require undue experimentation.

One useful assay utilizes a fusion peptide having maltose binding protein (MBP) fused to the C-terminal 125 amino acids of APP-SW. The MBP portion is captured on an assay substrate by anti-MBP capture antibody. Incubation of the captured fusion protein in the presence of beta-secretase results in cleavage of the substrate at the beta-secretase cleavage site. Analysis of the cleavage activity can be, for example, by immunoassay of cleavage products. One such immunoassay detects a unique epitope exposed at the carboxy terminus of the cleaved fusion protein, for example, using the antibody SW192. This assay is described, for example, in U.S. Patent No 5,942,400.

**Cellular assay**

Numerous cell-based assays can be used to analyze beta-secretase activity and/or processing of APP to release A beta.

5 Contact of an APP substrate with a beta-secretase enzyme within the cell and in the presence or absence of a compound inhibitor of the invention can be used to demonstrate beta-secretase inhibitory activity of the compound. Preferably, assay in the presence of a useful inhibitory compound provides at least

10 about 30%, most preferably at least about 50% inhibition of the enzymatic activity, as compared with a non-inhibited control.

In one embodiment, cells that naturally express beta-secretase are used. Alternatively, cells are modified to express a recombinant beta-secretase or synthetic variant

15 enzyme as discussed above. The APP substrate may be added to the culture medium and is preferably expressed in the cells. Cells that naturally express APP, variant or mutant forms of APP, or cells transformed to express an isoform of APP, mutant or variant APP, recombinant or synthetic APP, APP fragment, or

20 synthetic APP peptide or fusion protein containing the beta-secretase APP cleavage site can be used, provided that the expressed APP is permitted to contact the enzyme and enzymatic cleavage activity can be analyzed.

Human cell lines that normally process A beta from APP

25 provide a useful means to assay inhibitory activities of the compounds of the invention. Production and release of A beta and/or other cleavage products into the culture medium can be measured, for example by immunoassay, such as Western blot or enzyme-linked immunoassay (EIA) such as by ELISA.

30 Cells expressing an APP substrate and an active beta-secretase can be incubated in the presence of a compound inhibitor to demonstrate inhibition of enzymatic activity as compared with a control. Activity of beta-secretase can be measured by analysis of one or more cleavage products of the



APP substrate. For example, inhibition of beta-secretase activity against the substrate APP would be expected to decrease release of specific beta-secretase induced APP cleavage products such as A beta.

5 Although both neural and non-neural cells process and release A beta, levels of endogenous beta-secretase activity are low and often difficult to detect by EIA. The use of cell types known to have enhanced beta-secretase activity, enhanced processing of APP to A beta, and/or enhanced production of A  
10 beta are therefore preferred. For example, transfection of cells with the Swedish Mutant form of APP (APP-SW); with APP-KK; or with APP-SW-KK provides cells having enhanced beta-secretase activity and producing amounts of A beta that can be readily measured.

15 In such assays, for example, the cells expressing APP and beta-secretase are incubated in a culture medium under conditions suitable for beta-secretase enzymatic activity at its cleavage site on the APP substrate. On exposure of the cells to the compound inhibitor, the amount of A beta released  
20 into the medium and/or the amount of CTF99 fragments of APP in the cell lysates is reduced as compared with the control. The cleavage products of APP can be analyzed, for example, by immune reactions with specific antibodies, as discussed above.

Preferred cells for analysis of beta-secretase activity  
25 include primary human neuronal cells, primary transgenic animal neuronal cells where the transgene is APP, and other cells such as those of a stable 293 cell line expressing APP, for example, APP-SW.

30 **In vivo assays: animal models**

Various animal models can be used to analyze beta-secretase activity and /or processing of APP to release A beta, as described above. For example, transgenic animals expressing APP substrate and beta-secretase enzyme can be used

to demonstrate inhibitory activity of the compounds of the invention. Certain transgenic animal models have been described, for example, in U.S. Patent Nos: 5,877,399; 5,612,486; 5,387,742; 5,720,936; 5,850,003; 5,877,015,, and 5 5,811,633, and in Ganes et.al., 1995, Nature 373:523. Preferred are animals that exhibit characteristics associated with the pathophysiology of AD. Administration of the compound inhibitors of the invention to the transgenic mice described herein provides an alternative method for demonstrating the 10 inhibitory activity of the compounds. Administration of the compounds in a pharmaceutically effective carrier and via an administrative route that reaches the target tissue in an appropriate therapeutic amount is also preferred.

Inhibition of beta-secretase mediated cleavage of APP at 15 the beta-secretase cleavage site and of A beta release can be analyzed in these animals by measure of cleavage fragments in the animal's body fluids such as cerebral fluid or tissues. Analysis of brain tissues for A beta deposits or plaques is preferred.

20 On contacting an APP substrate with a beta-secretase enzyme in the presence of an inhibitory compound of the invention and under conditions sufficient to permit enzymatic mediated cleavage of APP and/or release of A beta from the substrate, the compounds of the invention are effective to 25 reduce beta-secretase-mediated cleavage of APP at the beta-secretase cleavage site and/or effective to reduce released amounts of A beta. Where such contacting is the administration of the inhibitory compounds of the invention to an animal model, for example, as described above, the compounds are 30 effective to reduce A beta deposition in brain tissues of the animal, and to reduce the number and/or size of beta amyloid plaques. Where such administration is to a human subject, the compounds are effective to inhibit or slow the progression of disease characterized by enhanced amounts of A beta, to slow

the progression of AD in the, and/or to prevent onset or development of AD in a patient at risk for the disease.

Unless defined otherwise, all scientific and technical terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are hereby incorporated by reference for all purposes.

#### DEFINITIONS

10 By "alkyl" and "C<sub>1</sub>-C<sub>6</sub> alkyl" in the invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. It is understood  
15 that in cases where an alkyl chain of a substituent (e.g. of an alkyl, alkoxy or alkenyl group) is shorter or longer than 6 carbons, it will be so indicated in the second "C" as, for example, "C<sub>1</sub>-C<sub>10</sub>" indicates a maximum of 10 carbons.

By "alkoxy" and "C<sub>1</sub>-C<sub>6</sub> alkoxy" in the invention is meant  
20 straight or branched chain alkyl groups having 1-6 carbon atoms, attached through at least one divalent oxygen atom, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, and 3-methylpentoxy.

25 By the term "halogen" in the invention is meant fluorine, bromine, chlorine, and iodine.

"Alkenyl" and "C<sub>2</sub>-C<sub>6</sub> alkenyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and from one to three double bonds and includes, for example, ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the  
30 like.

"Alkynyl" and "C<sub>2</sub>-C<sub>6</sub> alkynyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and one or

two triple bonds and includes ethynyl, propynyl, butynyl, pentyn-2-yl and the like.

As used herein, the term "cycloalkyl" refers to saturated carbocyclic radicals having three to twelve carbon atoms. The cycloalkyl can be monocyclic, or a polycyclic fused system. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such cycloalkyl groups may be optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl or di(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl.

By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl), which is optionally mono-, di-, or trisubstituted. Preferred aryl groups of the invention are phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, tetralinyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl. The aryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such aryl groups may be optionally substituted with, for example, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, -COOH, -C(=O)O(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(=O)NH<sub>2</sub>, -C(=O)N(mono- or di-C<sub>1</sub>-C<sub>6</sub> alkyl), -S(C<sub>1</sub>-C<sub>6</sub> alkyl), -SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), -O-C(=O)(C<sub>1</sub>-C<sub>6</sub> alkyl), -NH-C(=O)-(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(=O)-(C<sub>1</sub>-C<sub>6</sub> alkyl), -NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>

alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), -NH-C(=O)NH<sub>2</sub>, -NH-C(=O)N(mono- or di-C<sub>1</sub>-C<sub>6</sub> alkyl), -NH(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(=O)-NH<sub>2</sub> or -NH(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(=O)-N-(mono- or di-C<sub>1</sub>-C<sub>6</sub> alkyl).

By "heteroaryl" is meant one or more aromatic ring systems  
5 of 5-, 6-, or 7-membered rings which includes fused ring  
systems of 9-11 atoms containing at least one and up to four  
heteroatoms selected from nitrogen, oxygen, or sulfur.  
Preferred heteroaryl groups of the invention include pyridinyl,  
pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl,  
10 pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl,  
quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl,  
oxazolyl, thiazolyl, indoliziny, indazolyl, benzothiazolyl,  
benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl,  
oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl,  
15 oxazolopyridinyl, imidazopyridinyl, isothiazolyl,  
naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl,  
isochroman, chromanyl, tetrahydroisoquinolinyl, isoindolinyl,  
isobenzotetrahydrofuran, isobenzotetrahydrothienyl,  
isobenzothienyl, benzoxazolyl, pyridopyridinyl,  
20 benzotetrahydrofuran, benzotetrahydrothienyl, purinyl,  
benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl,  
pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl,  
dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl,  
dihydrobenzothiazinyl, benzopyran, benzothiopyran,  
25 coumarinyl, isocoumarinyl, chromon, chromanonyl, pyridinyl-N-  
oxide, tetrahydroquinolinyl, dihydroquinolinyl,  
dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl,  
dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl,  
benzoxazolinonyl, pyrrolyl N-oxide, pyrimidinyl N-oxide,  
30 pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide,  
indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide,  
quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-  
oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-  
oxide, thiazolyl N-oxide, indoliziny N-oxide, indazolyl N-

oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide. The heteroaryl groups herein are

5 unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such heteroaryl groups may be optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-

10 C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl or di(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, -COOH, -C(=O)O(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(=O)NH<sub>2</sub>, -C(=O)N(mono- or di-C<sub>1</sub>-C<sub>6</sub> alkyl), -S(C<sub>1</sub>-C<sub>6</sub> alkyl), -SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), -O-C(=O)(C<sub>1</sub>-C<sub>6</sub> alkyl), -NH-C(=O)-(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)-

15 C(=O)-(C<sub>1</sub>-C<sub>6</sub> alkyl), -NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), -NH-C(=O)NH<sub>2</sub>, -NH-C(=O)N(mono- or di-C<sub>1</sub>-C<sub>6</sub> alkyl), -NH(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(=O)-NH<sub>2</sub> or -NH(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(=O)-N-(mono- or di-C<sub>1</sub>-C<sub>6</sub> alkyl).

By "heterocycle", "heterocycloalkyl" or "heterocyclyl" is

20 meant one or more carbocyclic ring systems of 4-, 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heterocycles of the invention include morpholinyl, thiomorpholinyl,

25 thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranlyl, tetrahydrothienyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide,

30 oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide. Heterocycles may be fused to aryl rings. Examples include

tetrahydroisoquinoline and indoline. The heterocycle groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such heterocycle groups may be optionally substituted  
5 with C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl or =O.

10

All temperatures are in degrees Celsius.

TLC refers to thin-layer chromatography.

psi refers to pounds/in<sup>2</sup>.

HPLC refers to high pressure liquid chromatography.

15

THF refers to tetrahydrofuran.

DMF refers to dimethylformamide.

EDC refers to ethyl-1-(3-dimethylaminopropyl)carbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

HOBt refers to 1-hydroxy benzotriazole hydrate.

20

NMM refers to N-methylmorpholine.

NBS refers to N-bromosuccinimide.

TEA refers to triethylamine.

BOC refers to 1,1-dimethylethoxy carbonyl or t-butoxycarbonyl, -CO-O-C(CH<sub>3</sub>)<sub>3</sub>.

25

CBZ refers to benzyloxycarbonyl, -CO-O-CH<sub>2</sub>-phenyl.

Fmoc refers to 9-fluorenylmethyl carbonate.

TFA refers to trifluoroacetic acid.

CDI refers to 1,1'-carbonyldiimidazole.

Saline refers to an aqueous saturated sodium chloride  
30 solution.

Chromatography (column and flash chromatography) refers to purification/separation of compounds expressed as (support, eluent). It is understood that the appropriate fractions are pooled and concentrated to give the desired compound(s).

CMR refers to C-13 magnetic resonance spectroscopy, chemical shifts are reported in ppm ( $\delta$ ) downfield from TMS.

NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm ( $\delta$ ) downfield  
5 from TMS.

IR refers to infrared spectroscopy.

MS refers to mass spectrometry expressed as m/e, m/z or mass/charge unit.  $MH^+$  refers to the positive ion of a parent plus a hydrogen atom. EI refers to electron impact. CI refers  
10 to chemical ionization. FAB refers to fast atom bombardment.

HRMS refers to high resolution mass spectrometry.

Ether refers to diethyl ether.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a  
15 pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

When solvent pairs are used, the ratios of solvents used  
20 are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

25 TBDMSCl refers to t-butyldimethylsilyl chloride.

TBDMSOTf refers to t-butyldimethylsilyl trifluosulfonic acid ester.

Trisomy 21 refers to Down's Syndrome.

The following terms are used (in EXAMPLES 321 and above)  
30 for the amide forming agent (IX):

"PHTH" refers to  $(CH_3-CH_2-CH_2)_2N-CO-phenyl-CO-OH$  where the attachment to the - phenyl- ring is 1,3-;



"5-Me-PHTH" refers to  $(\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-})_2\text{N-CO-(CH}_3\text{-)}$  phenyl - CO-OH where the attachment to the - phenyl - ring is 1,3- for the carbonyl groups and 5- for the methyl group;

5 "3,5-pyridinyl" refers to  $(\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-})_2\text{N-CO-(pyridinyl)-}$  CO-OH where the attachment to the -pyridinyl- ring is 3,5- for the carbonyl groups;

"-SO<sub>2</sub>- " refers to  $(\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-})_2\text{CH-SO}_2\text{-}$  phenyl -CO-OH where the attachment to the - phenyl - ring is 1,3-;

10 "5-OMe-PHTH" refers to  $(\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-})_2\text{N-CO-(CH}_3\text{-O-)}$  phenyl -CO-OH where the attachment to the - phenyl - ring is 1,3- for the carbonyl groups and 5- for the methoxy group;

"5-Cl-PHTH" refers to  $(\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-})_2\text{N-CO-(Cl-)}$ phenyl-CO-OH where the attachment to the -phenyl- ring is 1,3- for the carbonyl groups and 5- for the chlorine atom;

15 "5-F-PHTH" refers to  $(\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-})_2\text{N-CO-(F-)}$ phenyl-CO-OH where the attachment to the -phenyl- ring is 1,3- for the carbonyl groups and 5- for the fluorine atom;

"thienyl" refers to  $(\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-})_2\text{N-CO-thienyl-CO-OH}$  where the attachment to the thiophene ring is -2,5;

20 "2,4-pyridinyl" refers to  $(\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-})_2\text{N-CO-(pyridinyl)-}$  CO-OH where the attachment to the -pyridinyl- ring is 2,4- for the carbonyl groups;

"4,6-pyrimidinyl" refers to  $(\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-})_2\text{N-CO-}$  (pyrimidinyl)-phenyl-CO-OH where the attachment to the - pyrimidinyl- ring is 4,6- for the carbonyl groups;

"morpholinyl" refers to morpholinyl-CO-phenyl-CO-OH where the attachment to the -phenyl- ring is 1,3 for the carbonyl groups.

30 APP, amyloid precursor protein, is defined as any APP polypeptide, including APP variants, mutations, and isoforms, for example, as disclosed in U.S. Patent No. 5,766,846.

A beta, amyloid beta peptide, is defined as any peptide resulting from beta-secretase mediated cleavage of APP, including peptides of 39, 40, 41, 42, and 43 amino acids, and

extending from the beta-secretase cleavage site to amino acids 39, 40, 41, 42, or 43.

Beta-secretase (BACE1, Asp2, Memapsin 2) is an aspartyl protease that mediates cleavage of APP at the amino-terminal edge of A beta. Human beta-secretase is described, for example, in W000/17369.

"Pharmaceutically acceptable" refers to those properties and/or substances that are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

A therapeutically effective amount is defined as an amount effective to reduce or lessen at least one symptom of the disease being treated or to reduce or delay onset of one or more clinical markers or symptoms of the disease.

The invention provides compounds, compositions, and methods for inhibiting beta-secretase enzyme activity and A beta peptide production. Inhibition of beta-secretase enzyme activity halts or reduces the production of A beta from APP and reduces or eliminates the formation of beta-amyloid deposits in the brain.

#### EXAMPLES

The following examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

PREPARATION 1 3-Amino-5-(methoxycarbonyl)benzoic acid (XVII)

A suspension of mono-methyl 5-nitro-isophthalate (22.5 g, 100 mmol) and palladium on carbon (5%, 2.00 g) in methanol (100 mL) is shaken in a hydrogenation apparatus under hydrogen (50 psi) for 3 hours. The mixture is then filtered through  
5 diatomaceous earth and concentrated to give the title compound, NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.67, 7.41, 7.40 and 3.83; MS (ESI-) for  $\text{C}_9\text{H}_9\text{NO}_4$   $m/z$   $(\text{M}-\text{H})^- = 194$ .

#### PREPARATION 2 3-Bromo-5-(methoxycarbonyl)benzoic acid (XIX)

10 A mixture of copper (II) bromide (1.85 g, 8.30 mmol), n-butyl nitrite (1.07 g, 10.4 mmol), and acetonitrile (30 mL) is stirred in a round bottomed flask in a water bath to which a few chunks of ice has been added. 3-Amino-5-(methoxycarbonyl)benzoic acid (XVII, PREPARATION 1, 1.35 g,  
15 6.92 mmol) is added as a slurry in warm acetonitrile (70 mL) over 15 min and the mixture is stirred at 20-25 degrees C for an additional 2 hour, at which time the mixture is partitioned between dichloromethane and hydrochloric acid (3N). The organic phase is separated and dried over sodium sulfate and  
20 concentrated to dryness. Chromatography (silica gel, 125 mL; methanol/dichloromethane, 15/85) and concentration of the appropriate fractions gives a solid which is crytallized from methanol to give the title compound in two crops, NMR ( $\text{DMSO}-d_6$ )  $\delta$  3.90, 8.26 and 8.65.

25

#### PREPARATION 3 Methyl

3-bromo-5-

[(dipropylamino)carbonyl]benzoate (XXI)

Carbonyl diimidazole (3.0 g, 18 mmol) is added to a solution of 3-bromo-5-(methoxycarbonyl)benzoic acid (XIX,  
30 PREPARATION 2, 3.9 g, 15 mmol) in THF (30 mL). The mixture is stirred for 0.5 hours. Dipropylamine (AMINE, 4.2 mL, 30 mmol) is added to the mixture, which is then stirred for 24 hours. The solvent is then removed under reduced pressure and the mixture is partitioned between ethyl acetate and water. The

organic phase is then washed with saline, dried over anhydrous magnesium sulfate, filtered, and concentrated. Column chromatography (silica gel; ethyl acetate/hexanes, 15/85) gives the title compound, IR (diffuse reflectance) 2968, 2958, 1714, 1637, 1479, 1440, 1422, 1321, 1310, 1288, 1273, 1252, 889, 772 and 718  $\text{cm}^{-1}$ ; NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21, 7.96, 7.70, 3.95, 3.46, 3.15, 1.69, 1.57, 1.00 and 0.78; MS (ESI+) for  $\text{C}_{15}\text{H}_{20}\text{BrNO}_3$   $m/z$   $(\text{M}+\text{H})^+ = 344.1$ .

10 PREPARATION 4 3-Bromo-5-[(dipropylamino)carbonyl]benzoic acid  
To a solution of methyl 3-bromo-5-[(dipropylamino)carbonyl]benzoate (XXI, PREPARATION 3, 1.4 g, 4.1 mmol) in THF/water/methanol (4/2/2, 8 mL) is added to lithium hydroxide monohydrate (0.17 g, 4.05 mmol). The mixture  
15 is stirred at 20 degrees -25 degrees C for 1 hour and then solvent is removed under reduced pressure. The residue is dissolved in water (50 mL) and hydrochloric acid (1 N) is added to adjust the pH to about 3. The aqueous mixture is extracted with ethyl acetate and the organic phase is separated and dried  
20 over magnesium sulfate to give the title compound. Analytical calculated for  $\text{C}_{14}\text{H}_{18}\text{BrNO}_3$ : C, 51.23; H, 5.53; N, 4.27; Br, 24.35. Found: C, 51.37; H, 5.56; N, 4.28.

PREPARATION 5 Methyl 3-(aminocarbonyl)-5-[(dipropylamino)carbonyl]-benzoate (XXII)  
25 To a mixture of methyl 3-bromo-5-[(dipropylamino)carbonyl]benzoate (XXI, PREPARATION 3, 0.5 g, 1.47 mmol) in dry N-methyl pyrrolidinone under a carbon monoxide atmosphere is added palladium (II) acetate (0.017 g, 0.074 mmol), 1,3-bis(diphenylphosphino)propane (0.045 g, 0.11 mmol), hexamethyldisilazane (1.0 mL, 4.7 mmol), and diisopropylethylamine (0.38 g, 2.94 mmol). The mixture is heated at 100 degrees C for 24 hours. The mixture is cooled to 20-25 degrees C and partitioned between water and ethyl

acetate. The layers are separated and the aqueous phase is back-washed with ethyl acetate. The organic phases are combined and washed three times with saline, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography (silica gel, 75 mL; methanol/methylene chloride, 2.5/97.5) gives the title compound, NMR (CDCl<sub>3</sub>) delta 0.77, 1.02, 1.57, 1.71, 3.17, 3.49, 3.98, 5.78, 6.34, 8.07, 8.20 and 8.48.

10 PREPARATION 6 3-(Aminocarbonyl)-5-  
[(dipropylamino)carbonyl]benzoic acid (XXIII)

To a mixture of methyl 3-(aminocarbonyl)-5-[(dipropylamino)carbonyl]benzoate (XXII, PREPARATION 5, 0.197 g, 0.64 mmol) in methanol (5.0 mL) is added sodium hydroxide (1N, 3.0 mL). The mixture is stirred at 20-25 degrees C for 24 hours. The mixture is acidified to about pH 5 with hydrochloric acid (10%). Water (50 mL) is added and the mixture is washed twice with ethyl acetate (2 x 50 mL). The organic extracts are combined and dried over anhydrous magnesium sulfate and concentrated to give the title compound, NMR (DMSO-d<sub>6</sub>) delta 0.66, 0.930, 1.48, 1.62, 3.12, 3.35, 7.54, 7.98, 8.22 and 8.51.

25 PREPARATION 7 3-Cyano-5-[(dipropylamino)carbonyl]benzoic acid (IX/XXXII)

A mixture of 3-bromo-5-[(dipropylamino)carbonyl]benzoic acid (PREPARATION 4, 0.596 g, 1.82 mmol) and copper nitrile (0.325 g, 3.63 mmol) in N-methylpyrrolidinone (1.5 mL) is stirred at 175 degrees C for 2.5 hour, at which time the mixture is cooled and partitioned between ethyl acetate and hydrochloric acid (3N). The organic layer is washed twice more with hydrochloric acid (3N) and then twice more with saline which had been acidified with a small amount of hydrochloric

acid (3N). The organic layer is dried over magnesium sulfate and concentrated under high vacuum to give the title compound, NMR (CDCl<sub>3</sub>) delta 0.80, 1.02, 1.60, 1.73, 3.17, 3.51, 7.90, 8.31 and 8.41; an aliquot is crystallized from ethyl ether/dichloromethane/hexane - IR (diffuse reflectance) 3017, 2970, 2937, 2898, 2877, 2473, 2432, 2350, 2318, 2236, 1721, 1608, 1588, 1206 and 1196 cm<sup>-1</sup>.

PREPARATION 8 3-(Aminocarbonyl)-5-  
10 [(dipropylamino)carbonyl]benzoic acid (XXXIII)

A mixture of 3-cyano-5-[(dipropylamino)carbonyl]benzoic acid (IX/XXXII, PREPARATION 7, 0.602 g, 2.19 mmol), potassium carbonate (0.212 g, 1.53 mmol), and acetone (2.5 mL) is stirred  
15 at 20-25 degrees C. Water (2.5 mL) and urea-hydrogen peroxide adduct (0.825 g, 8.78 mmol) are added and the mixture is stirred for 15 hours at 20-25 degrees C, at which time additional urea-hydrogen peroxide adduct (0.204 g) is added; after stirring for another 3 hours, an additional 0.205 g of  
20 urea-hydrogen peroxide is added. After a total of 39 hours has elapsed, the acetone is removed under reduced pressure and the residue is acidified with hydrochloric acid (3N) to pH = 2-4. The mixture is extracted with dichloromethane, the organic layer is separated and washed with hydrochloric acid (0.5 N),  
25 and the organic phase is dried with anhydrous magnesium sulfate to a solid. The solid is crystallized from dichloromethane/hexane/methanol to give the title compound, MS (ESI+) for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub> m/z (M+H)<sup>+</sup> = 293.2.

30 PREPARATION 9 Methyl 3-[(dipropylamino)carbonyl]-5-nitrobenzoate (XXX)

Carbonyl diimidazole (3.90 g, 24.0 mmol) is added to a mixture of mono-methyl 5-nitro-isophthalate (XXVIII, 4.50 g, 20.0 mmol) in dry THF (50 mL). The mixture is stirred for 0.5

hours. Dipropylamine (3.28 mL, 24.0 mmol) is added slowly to the mixture. The reaction mixture is then stirred for 4 hours. The solvent is removed under reduced pressure and the mixture is partitioned between ethyl acetate and water. The organic phase is separated and washed with saline, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (silica gel; ethyl acetate/hexanes, 15/85) gives the title compound, NMR (300 MHz, CDCl<sub>3</sub>) delta 8.88, 8.41, 8.35, 4.00, 3.48, 3.15, 1.72, 1.57, 1.00 and 0.77; MS (ESI+) for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub> m/z (M+H)<sup>+</sup> = 309.2.

PREPARATION 10                  Methyl                                  3-amino-5-

[ (dipropylamino) carbonyl] benzoate (XXXI)

A suspension of methyl 3-[(dipropylamino)carbonyl]-5-nitrobenzoate (XXX, PREPARATION 9, 6.00g, 20.0 mmol) and palladium on carbon (5%, 0.600 g) in methanol (40 mL) is shaken in a hydrogenation apparatus under hydrogen (45 psi) for 3 hours. The mixture is then filtered through diatomaceous earth and concentrated to give the title compound, NMR (300 MHz, CDCl<sub>3</sub>) delta 7.27, 6.77, 4.10, 3.82, 3.38, 3.10, 1.62, 1.46, 0.91 and 0.68.

PREPARATION 11                  Methyl                                  3-(chlorosulfonyl)-5-  
[ (dipropylamino) carbonyl ] - benzoate (XXXVII)

25 Methyl 3-amino-5-[(dipropylamino)carbonyl]benzoate (XXXI,  
PREPARATION 10, 1.11 g, 4 mmol) is added to a mixture of water  
(5 mL) and concentrated hydrochloric acid (1 mL). Sodium  
nitrite (0.276 g, 4 mmol) is added to the mixture slowly at 0  
degrees C. The mixture is then added to an acetic acid  
30 solution (5 mL) of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  saturated with sulfur dioxide.  
The mixture is stirred for 0.5 hours and poured into ice water.  
The mixture is extracted with ethyl acetate. The organic phase  
is separated and washed with saturated sodium bicarbonate,  
water, and saline and dried over anhydrous sodium sulfate,





$J = 7$  Hz, 2 H), 1.71 (m, 2 H), 1.55 (m, 2 H), 0.97 (t,  $J = 7$  Hz, 3 H), 0.74 (t,  $J = 7$  Hz, 3 H). MS (ESI+) for  $C_{11}H_{20}N_2O_5S$   $m/z$  329.2 (M+H)<sup>+</sup>.

5 PREPARATION 14 Methyl 3-[(dipropylamino)carbonyl]-5-(1-pyrrolidinylsulfonyl)- benzoate (XXXVIII)

Following the general procedure of PREPARATION 12 and making non-critical variations but using pyrrolidine (0.347 mL, 4.16 mmol), the title compound is obtained, MS (ESI+) for  
10  $C_{19}H_{28}N_2O_5S$   $m/z$  (M+H)<sup>+</sup> = 397.1.

PREPARATION 15 3-[(Dipropylamino)carbonyl]-5-(1-pyrrolidinylsulfonyl)benzoic acid (XXXIX)

Following the general procedure of PREPARATION 13 and  
15 making non-critical variations, the title compound is obtained, MS (ESI+) for  $C_{18}H_{26}N_2O_5S$   $m/z$  (M+H)<sup>+</sup> = 383.3.

PREPARATION 16 Methyl 3-[(dipropylamino)carbonyl]-5-[(methylamino)-sulfonyl]benzoate (XXXVIII)

20 Following the general procedure of PREPARATION 12 and making non-critical variations but using methyl amine (2 N solution in THF, 0.692 mL, 1.38 mmol), the title compound is obtained, MS (ESI+) for  $C_{16}H_{24}N_2O_5S$   $m/z$  (M+H)<sup>+</sup> = 357.1.

25 PREPARATION 17 3-[(Dipropylamino)carbonyl]-5-[(methylamino)- sulfonyl]benzoic acid (XXXIX)

Following the general procedure of PREPARATION 13 and making non-critical variations, the title compound is obtained, MS (ESI+) for  $C_{15}H_{22}N_2O_5S$   $m/z$  (M+H)<sup>+</sup> = 343.1.

30

PREPARATION 18 Methyl 3-[(dimethylamino)sulfonyl]-5-[(dipropylamino)- carbonyl]benzoate (XXXVIII)

Following the general procedure of PREPARATION 12 and making non-critical variations but using dimethylamine (2 N

solution in THF, 0.692 mL, 1.38 mmol), the title compound is obtained, MS (ESI+) for  $C_{17}H_{26}N_2O_5S$   $m/z$   $(M+H)^+ = 371.1$ .

PREPARATION 19 3-[(Dimethylamino)sulfonyl]-5-

5 [(dipropylamino)carbonyl]-benzoic acid (XXXIX)

Following the general procedure of PREPARATION 13 and making non-critical variations, the title compound is obtained, MS (ESI+) for  $C_{16}H_{24}N_2O_5S$   $m/z$   $(M+H)^+ = 357.1$ .

10 PREPARATION 20 Methyl 3-[(dipropylamino)carbonyl]-5-ethylbenzoate (IX)

Ethylboronic acid (0.800 g, 10.8 mmol), dichlorobis(triphenylphosphine)-palladium(II) (0.252 g, 0.360 mmol), potassium carbonate (2.50 g, 18.0 mmol) and lithium chloride (0.151 g, 3.60 mmol) are added to a mixture of methyl 3-bromo-5-[(dipropylamino)carbonyl]benzoate (1.23 g, 3.60 mmol) in dry DMF (20 mL). The mixture is heated at 100 degrees C for 18 hours. The mixture is then partitioned between ethyl acetate and water. The phases are separated and the ethyl acetate phase is washed with saline, dried over sodium sulfate and concentrated. The concentrate is column chromatographed (silica gel; ethyl acetate/hexanes, 15/85) to give the title compound, MS (ESI+) for  $C_{17}H_{25}NO_3$   $m/z$   $(M+H)^+ = 292.2$ .

25 PREPARATION 21 3-[(Dipropylamino)carbonyl]-5-ethylbenzoic acid (IX)

Lithium hydroxide monohydrate (0.0680 g, 1.6 mmol) is added to a mixture of methyl 3-[(dipropylamino)carbonyl]-5-ethylbenzoate (PREPARATION 20, 0.450 g, 1.6 mmol) in a mixture of THF/methanol/water (2/1/1, 8 mL). The mixture is stirred at 20-25 degrees C for 3 hours. The mixture is then diluted with water (20 mL) and hydrochloric acid (1 N) is added to bring the pH to less than 3. The aqueous mixture is extracted with ethyl acetate. The organic phase is separated and washed with

saline, dried over anhydrous magnesium sulfate, filtered and concentrated to give the title compound, MS (ESI+) for  $C_{16}H_{23}NO_3$   $m/z$   $(M+H)^+ = 278.2$ .

5   EXAMPLE 1           tert-Butyl (1S)-3-bromo-1-(3,5-difluorobenzyl)-  
                          2-oxopropylcarbamate (III)

                  N-methyl-morpholine (5.83 mL, 53 mmole, 1.05 eq.) is added to (2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,5-difluorophenyl)propanoic acid (II, 15 g, 50 mmole) in THF (100  
10 mL) and the reaction is cooled to -78 degrees C. Isobutyl chloroformate (6.87 mL, 53 mmole, 1.05 eq.) is added rapidly. The cold bath is then removed and the mixture stirred for 1 hour. The reaction is monitored by TLC to insure completion of the reaction and the mixture is then filtered and washed with  
15 dry THF (50 ml) and kept cold in the filtered flask at -20 degrees C.

                  In an ice-salt bath is placed a 500 ml graduate cylinder containing ether (200 mL) and aqueous potassium hydroxide (40%, 60 ml). 1-Methyl-3-nitro-1-nitrosoguanidine (5.6 g, 106 mmole,  
20 2.1 eq.) is added slowly with stirring and temperature kept below 0 degrees C. The mixture turned yellow and the bubbling lasted for 10 minutes. The stirring is stopped and without mixing the layers, the top diazomethane ethereal layer is transferred with non-ground tip pipette into the stirred mixed  
25 anhydride mixture at -20 degrees C. The reaction is monitored by TLC (ethyl acetate/hexane, 50/50;  $R_f = 0.69$ ). After 1 hour nitrogen is then bubbled into the mixture. The solvent is removed under reduced pressure (with heat) and the mixture is partitioned between ether and water. The phases are separated,  
30 the organic phase is washed with bicarbonate, saline, dried over anhydrous sodium sulfate and solvent removed under reduced pressure (with heat). The residue is dissolved in ether (100 mL) and hydrobromic acid (48%, 15 mL, 135 mmole, 2.7 eq.) is added at -20 degrees C, the cold bath is removed and the

mixture is stirred for another 0.5 hours. The reaction is monitored by TLC (ethyl acetate/hexane, 50/50;  $R_f$  = 0.88). The mixture is partitioned between ether and water, washed with bicarbonate, saline, dried over anhydrous sodium sulfate and the solvent removed. The residue is recrystallized from ethanol to give the title compound, TLC (ethyl acetate/hexane, 50/50)  $R_f$  = 0.88; MS ( $MH^+$ ) = 379.3.

10 EXAMPLE 2        *tert*-Butyl        (1*S*,        2*S*)-3-bromo-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV)

Sodium borohydride (1.32 g, 34.9 mmole, 1.1 eq.) is added to *tert*-Butyl (1*S*)-3-bromo-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate (III, EXAMPLE 1, 12 g, 31.75 mmole) dissolved in absolute alcohol (500 mL) at -78 degrees C. The reaction mixture is stirred for 0.5 hour and monitored by TLC (ethyl acetate/hexane, 20/80;  $R_f$  = 0.2). The mixture is quenched with water (10 mL) and the solvent removed under reduced pressure with heat (not exceeding 30 degrees C) to dryness. The solid is partitioned between dichloromethane and water, washed with saline, dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure to give the title compound, TLC (ethyl acetate/hexane, 20/80)  $R_f$  = 0.2; MS ( $MH^+$ ) = 381.2.

25 EXAMPLE 3        *tert*-Butyl (1*S*)-2-(3,5-difluorophenyl)-1-[(2*S*)-oxiranyl]ethylcarbamate (V)

*tert*-Butyl (1*S*, 2*S*)-3-bromo-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV, EXAMPLE 2) is dissolved in absolute alcohol (150 mL) and ethyl acetate (100 mL) and potassium hydroxide (2.3 g, 34.9 mmole, 1.1eq.) in ethyl alcohol (85%, 5mL) is added at -20 degrees C. The cold bath is then removed and the mixture stirred for 0.5 hour. The reaction is monitored by TLC (ethyl acetate/hexane, 20/80). When the reaction is complete, it is diluted with dichloromethane and

extracted, washed with water, saline, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The crude material is purified by flash chromatography on silica gel to give the title compound, TLC (ethyl acetate/hexane, 20/80)  $R_f = 0.3$ ; MS ( $MH^+$ ) = 300.4.

EXAMPLE 4      tert-Butyl (1S, 2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (VII)

10      tert-Butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3, 245 mg, 0.82 mmol) is suspended in isopropyl alcohol (6 mL) and 3-methoxybenzylamine (160 microL, 1.22 mmol) is added with stirring at 20-25 degrees C. This mixture is heated to gentle reflux (bath temp 85  
15 degrees C) under nitrogen for 2 hours, whereupon the resulting mixture is concentrated under reduced pressure to give the title compound. The title compound is purified by flash chromatography (2-5% methanol/methylene chloride; gradient elution) to give purified title compound.

20

EXAMPLE 5      (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxybenzyl)amino]-2-butanol trifluoroacetate (VIII)

tert-Butyl (1S, 2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-  
25 [(3-methoxybenzyl)amino]propylcarbamate (VII, EXAMPLE 4, 258 mg, 0.59 mmol) is dissolved in methylene chloride (1 mL) at 20-25 degrees C, and trifluoroacetic acid (1 mL) is added with stirring under nitrogen. The reaction mixture is stirred at 20-25 degrees C for 1 hour, whereupon the reaction mixture is  
30 concentrated under reduced pressure to give the title compound. The title compound is used in the next reaction without further purification.

EXAMPLE 6  $N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-  
[(3-methoxybenzyl)amino]propyl}-5-methyl- $N^3,N^3$ -  
dipropylisophthalamide (X)

(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-  
5 methoxybenzyl)amino]-2-butanol trifluoroacetate salt (VIII,  
EXAMPLE 5) is dissolved in anhydrous DMF (3 mL) and cooled to 0  
degrees C. Triethylamine (500 microliter, 3.6 mmol) and 5-  
methyl-N, N-dipropylisophthalamic acid (156 mg, 0.59 mmol) are  
added with stirring. The mixture is warmed to 20-25 degrees C  
10 briefly to allow for complete dissolution of the carboxylic  
acid, before recooling to 0 degrees C. 1-Hydroxybenzotriazole  
(157 mg, 1.2 mmol) is added with stirring, followed by 1-(3-  
dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (229 mg,  
1.2 mmol). The resulting mixture is stirred at 0 degrees C for  
15 5 minutes, then warmed to 20-25 degrees C for 15 hours. The  
reaction mixture is then quenched with aqueous citric acid  
(10%), and the mixture extracted three times with ethyl  
acetate. The combined organic extracts are washed with  
saturated sodium bicarbonate, saline, dried over sodium  
20 sulfate, filtered and concentrated under reduced pressure to  
give the the title compound in crude form. This material is  
purified by flash chromatography (2-10% methanol/methylene  
chloride gradient elution) to give purified title compound, MS  
(ES)  $MH^+$  = 582.3.

25

## EXAMPLES 7-9

Following the general procedure of EXAMPLE 1 and making  
non critical variations but starting with the protecting group  
of Column A and using the acid of Column B, the protected  
30 compound (III) of Column C is obtained:

EXAMPLE	Column A	Column B	Column C
7	BOC	Hydrochloric	tert-butyl (1S)-3-chloro- 1-(3,5-difluorobenzyl)-2- oxopropylcarbamate

8	CBZ	Hydrobromic	benzyl (1S)-3-bromo-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate
9	CBZ	Hydrochloric	benzyl (1S)-3-chloro-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate

## EXAMPLES 10-12

Following the general procedure of EXAMPLE 2 and making non critical variations but starting with the protected compound (III) of Column A, the alcohol (IV) of Column B is obtained:

EXAMPLE	Column A	Column B
10	7	Tert-butyl (1S, 2S)-3-chloro-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate
11	8	Benzyl (1S, 2S)-3-bromo-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate
12	9	Benzyl (1S, 2S)-3-chloro-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate

EXAMPLE 13      Benzyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V)

Following the general procedure of EXAMPLE 3 and making non critical variations but starting with the alcohol (IV) of EXAMPLE 12, the title compound is obtained.

## EXAMPLES 14-107

Following the general procedure of EXAMPLE 4 and making non-critical variations but reacting tert-butyl (1S,2S)-1-(2-oxiranyl)-2-phenylethylcarbamate (V, commercially available) with the C-terminal amine (VI) of Column A, the protected alcohol (VII) of Column B is obtained.

Examp e No.	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
14	H <sub>2</sub> N-CH <sub>2</sub> CH <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-3-(ethylamino)-2-hydroxypropylcarbamate

15	H <sub>2</sub> N-CH <sub>2</sub> -phenyl	tert-butyl (1S,2R)-1-benzyl-3-(benzylamino)-2-hydroxypropylcarbamate
16	H <sub>2</sub> N-CH(CH <sub>3</sub> ) <sub>2</sub>	tert-butyl (1S,2R)-1-benzyl-3-(isopropylamino)-2-hydroxypropylcarbamate
17	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-4-CH <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(4-methylbenzyl)amino]propylcarbamate
18	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -phenyl-4-OCH <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[2-(4-methoxyphenyl)ethyl]amino]propylcarbamate
19	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3-OCH <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
20	H <sub>2</sub> N-CH(-phenyl)-CO-OC <sub>2</sub> H <sub>5</sub>	ethyl ((2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-4-phenylbutyl)amino(phenyl)acetate
21	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -phenyl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-phenylethyl)amino]propylcarbamate
22	H <sub>2</sub> N-CH(-CH <sub>2</sub> OH)-CH(OH)-phenyl-4-NO <sub>2</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[1S)-2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]amino]propylcarbamate
23	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-2-Cl	tert-butyl (1S,2R)-1-benzyl-3-[(2-chlorobenzyl)amino]-2-hydroxypropylcarbamate
24	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-4-Cl	tert-butyl (1S,2R)-1-benzyl-3-[(4-chlorobenzyl)amino]-2-hydroxypropylcarbamate
25	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -O-(CH <sub>2</sub> ) <sub>2</sub> -OH	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[2-(2-hydroxyethoxy)ethyl]amino]propylcarbamate
26	H <sub>2</sub> N-1-indanyl	tert-butyl (1S,2R)-1-benzyl-3-(2,3-dihydro-1H-inden-1-ylamino)-2-hydroxypropylcarbamate
27	H <sub>2</sub> N-CH <sub>2</sub> -CH(OH)-CH <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-hydroxypropyl)amino]propylcarbamate
28	H <sub>2</sub> N-CH <sub>2</sub> -tetrahydrofuran-1	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(tetrahydro-2-furanylmethyl)amino]propylcarbamate



29	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}(-\text{OCH}_2\text{CH}_3)$	tert-butyl (1S,2R)-1-benzyl-3-[(2,2-diethoxyethyl)amino]-2-hydroxypropylcarbamate
30	$\text{H}_2\text{N}-(\text{CH}_2)_4-\text{CH}_3$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-(pentylamino)propylcarbamate
31	$\text{H}_2\text{N}-\text{cyclohexyl}$	tert-butyl (1S,2R)-1-benzyl-3-(cyclohexylamino)-2-hydroxypropylcarbamate
32	$\text{H}_2\text{N}-\text{CH}_2-\text{pyridin-2-yl}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-pyridinylmethyl)amino]propylcarbamate
33	$\text{H}_2\text{N}-\text{CH}_2-\text{phenyl-2-NH}_2$	tert-butyl (1S,2R)-3-[(2-aminobenzyl)amino]-1-benzyl-2-hydroxypropylcarbamate
34	$\text{H}_2\text{N}-\text{CH}_2-\text{pyridin-3-yl}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-pyridinylmethyl)amino]propylcarbamate
35	$\text{H}_2\text{N}-(\text{CH}_2)_2-\text{pyrrolidin-1-yl}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[2-(1-pyrrolidinyl)ethyl]amino]propylcarbamate
36	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}(\text{OH})-\text{phenyl}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-hydroxy-2-phenylethyl)amino]propylcarbamate
37	$\text{H}_2\text{N}-(\text{CH}_2)_3-\text{O}-(\text{CH}_2)_3-\text{CH}_3$	tert-butyl (1S,2R)-1-benzyl-3-[(3-butoxypropyl)amino]-2-hydroxypropylcarbamate
38	$\text{H}_2\text{N}-(\text{CH}_2)_3-\text{O}-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-isopropoxypropyl)amino]propylcarbamate
39	$\text{H}_2\text{N}-(\text{CH}_2)_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-(isopentylamino)propylcarbamate
40	$\text{H}_2\text{N}-(\text{CH}_2)_3-\text{phenyl}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-phenylpropyl)amino]propylcarbamate
41	$\text{H}_2\text{N}-(\text{CH}_2)_2-\text{OCH}_3$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-methoxyethyl)amino]propylcarbamate
42	$\text{H}_2\text{N}-(\text{CH}_2)_2-\text{O-phenyl}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-phenoxyethyl)amino]propylcarbamate
43	$\text{H}_2\text{N}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{CH}_3$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-propoxyethyl)amino]propylcarbamate

44	$\text{H}_2\text{N}-(\text{CH}_2)_2-\text{C}(\text{CH}_3)_3$	tert-butyl (1S,2R)-1-benzyl-3-[(3,3-dimethylbutyl)amino]-2-hydroxypropylcarbamate
45	$\text{H}_2\text{N}-(\text{CH}_2)_4\text{-phenyl}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(4-phenylbutyl)amino]propylcarbamate
46	$\text{H}_2\text{N}-\text{CH}_2\text{-phenyl-3-I}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-iodobenzyl)amino]propylcarbamate
47	$\text{H}_2\text{N}-\text{CH}_2\text{-phenyl-4-NO}_2$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(4-nitrobenzyl)amino]propylcarbamate
48	$\text{H}_2\text{N}-\text{CH}_2\text{-phenyl-3-Cl}$	tert-butyl (1S,2R)-1-benzyl-3-[(3-chlorobenzyl)amino]-2-hydroxypropylcarbamate
49	$\text{H}_2\text{N}-(\text{CH}_2)_2\text{-phenyl-4-Cl}$	tert-butyl (1S,2R)-1-benzyl-3-[[2-(4-chlorophenyl)ethyl]amino]-2-hydroxypropylcarbamate
50	$\text{H}_2\text{N}-(\text{CH}_2)_2\text{-pyridin-2-yl}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[2-(2-pyridinyl)ethyl]amino]propylcarbamate
51	$\text{H}_2\text{N}-\text{CH}_2\text{-pyridin-4-yl}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(4-pyridinylmethyl)amino]propylcarbamate
52	$\text{H}_2\text{N}-(\text{CH}_2)_2\text{-(N-methylpyrrolidin-2-yl)}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[2-(1-methyl-2-pyrrolidinyl)ethyl]amino]propylcarbamate
53	$\text{H}_2\text{N}-\text{CH}_2\text{-phenyl-2,3-dimethyl}$	tert-butyl (1S,2R)-1-benzyl-3-[(2,3-dimethylbenzyl)amino]-2-hydroxypropylcarbamate
54	$\text{H}_2\text{N}-\text{CH}_2\text{-phenyl-2-OCF}_3$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[2-(trifluoromethoxy)benzyl]amino]propylcarbamate
55	$\text{H}_2\text{N}-\text{CH}_2\text{-phenyl-2-Cl-6-O-phenyl}$	tert-butyl (1S,2R)-1-benzyl-3-[(2-chloro-6-phenoxybenzyl)amino]-2-hydroxypropylcarbamate
56	$\text{H}_2\text{N}-\text{CH}_2\text{-phenyl-4-CF}_3$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[4-(trifluoromethyl)benzyl]amino]propylcarbamate
57	$\text{H}_2\text{N}-\text{CH}_2\text{-phenyl-2,3-dichloro}$	tert-butyl (1S,2R)-1-benzyl-3-[(2,3-dichlorobenzyl)amino]-2-hydroxypropylcarbamate
58	$\text{H}_2\text{N}-\text{CH}_2\text{-phenyl-3,5-dichloro}$	tert-butyl (1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropylcarbamate

59	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3,5-difluoro	tert-butyl (1S,2R)-1-benzyl-3-[(3,5-difluorobenzyl)amino]-2-hydroxypropylcarbamate
60	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-4-OCF <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[4-(trifluoromethoxy)benzyl]amino]propylcarbamate
61	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -phenyl-4-SO <sub>2</sub> -NH <sub>2</sub>	tert-butyl (1S,2R)-3-[[4-(aminosulfonyl)benzyl]amino]-1-benzyl-2-hydroxypropylcarbamate
62	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-4-OCH <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(4-methoxybenzyl)amino]propylcarbamate
63	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-4-CH <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(4-methylbenzyl)amino]propylcarbamate
64	H <sub>2</sub> N-CH <sub>2</sub> -Ph-(3,4,5-trimethoxy)	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3,4,5-trimethoxybenzyl)amino]propylcarbamate
65	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3-OCF <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[3-(trifluoromethoxy)benzyl]amino]propylcarbamate
66	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3,5-dimethoxy	tert-butyl (1S,2R)-1-benzyl-3-[(3,5-dimethoxybenzyl)amino]-2-hydroxypropylcarbamate
67	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-2,4-dimethoxy	tert-butyl (1S,2R)-1-benzyl-3-[(2,4-dimethoxybenzyl)amino]-2-hydroxypropylcarbamate
68	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-phenyl	tert-butyl (1S,2R)-1-benzyl-3-[[[1,1'-biphenyl]-3-ylmethyl]amino]-2-hydroxypropylcarbamate
69	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3,4-dichloro	tert-butyl (1S,2R)-1-benzyl-3-[(3,4-dichlorobenzyl)amino]-2-hydroxypropylcarbamate
70	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-4-F	tert-butyl (1S,2R)-1-benzyl-3-[(4-fluorobenzyl)amino]-2-hydroxypropylcarbamate
71	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3-CF <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propylcarbamate
72	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-2-CH <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-methylbenzyl)amino]propylcarbamate

73	H <sub>2</sub> N-CH((R)-CH <sub>3</sub> )-phenyl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[(1R)-1-phenylethyl]amino}propylcarbamate
74	H <sub>2</sub> N-CH((S)-CH <sub>3</sub> )-phenyl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[(1S)-1-phenylethyl]amino}propylcarbamate
75	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3,5-(bis)trifluoromethyl	tert-butyl (1S,2R)-1-benzyl-3-{{[3,5-bis(trifluoromethyl)benzyl]amino}-2-hydroxypropylcarbamate
76	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-2-CF <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{{[2-(trifluoromethyl)benzyl]amino}propylcarbamate
77	H <sub>2</sub> N-CH((S)-CH <sub>3</sub> )-(naphth-1-yl)	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[(1S)-1-(1-naphthyl)ethyl]amino}propyl carbamate
78	-NH <sub>2</sub> -CH((R)-CH <sub>3</sub> )-(naphth-1-yl)	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propylcarbamate
79	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3-OCH <sub>3</sub> -4-OH	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[4-hydroxy-3-methoxybenzyl]amino]propylcarbamate
80	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3,4-dihydroxy	tert-butyl (1S,2R)-1-benzyl-3-[[3,4-dihydroxybenzyl]amino]-2-hydroxypropylcarbamate
81	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>3</sub> -OCH <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[3-methoxypropyl]amino]propylcarbamate
82	H <sub>2</sub> N-CH((S)-CH <sub>3</sub> )-CH <sub>2</sub> -OH	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[(1S)-2-hydroxy-1-methylethyl]amino}propyl carbamate
83	H <sub>2</sub> N-CH((R)-CH <sub>3</sub> )-CH <sub>2</sub> -OH	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[(1R)-2-hydroxy-1-methylethyl]amino}propyl carbamate
84	H <sub>2</sub> N-CH <sub>2</sub> -C≡CH	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-(2-propynylamino)propylcarbamate
85	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -phenyl-2-F	tert-butyl (1S,2R)-1-benzyl-3-{{[2-(2-fluorophenyl)ethyl]amino}-2-hydroxypropylcarbamate
86	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -phenyl-3-F	tert-butyl (1S,2R)-1-benzyl-3-{{[2-(3-fluorophenyl)ethyl]amino}-2-hydroxypropyl carbamate

87	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -phenyl-4-F	tert-butyl (1S,2R)-1-benzyl-3-{{[2-(4-fluorophenyl)ethyl] amino}-2-hydroxypropyl carbamate
88	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -phenyl-4-Br	tert-butyl (1S,2R)-1-benzyl-3-{{[2-(4-bromophenyl)ethyl] amino}-2-hydroxypropyl carbamate
89	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -phenyl-3-OCH <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{{[2-(3-methoxyphenyl)ethyl] amino}propyl carbamate
90	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -phenyl-2,4-dichloro	tert-butyl (1S,2R)-1-benzyl-3-{{[2-(2,4-dichlorophenyl)ethyl] amino}-2-hydroxypropyl carbamate
91	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -phenyl-3-Cl	tert-butyl (1S,2R)-1-benzyl-3-{{[2-(3-chlorophenyl)ethyl] amino}-2-hydroxypropyl carbamate
92	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -phenyl-2,5-dimethoxy	tert-butyl (1S,2R)-1-benzyl-3-{{[2-(2,5-dimethoxyphenyl)ethyl] amino}-2-hydroxypropyl carbamate
93	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -phenyl-4-CH <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{{[2-(4-methylphenyl)ethyl] amino}propyl carbamate
94	H <sub>2</sub> N-CH(-R)CH <sub>2</sub> -OH)-CH <sub>2</sub> -phenyl	tert-butyl (1S,2R)-1-benzyl-3-{{[(1R)-1-benzyl-2-hydroxyethyl] amino}-2-hydroxypropyl carbamate
95	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>3</sub> -(1-morpholinyl)	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{{[3-(4-morpholinyl)propyl] amino}propyl carbamate
96	H <sub>2</sub> N-CH <sub>2</sub> -C(CH <sub>3</sub> ) <sub>2</sub>	tert-butyl (1S,2R)-1-benzyl-3-{{[(3,3-dimethylbutyl) amino]-2-hydroxypropyl carbamate
97	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -(1-morpholinyl)	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{{[2-(4-morpholinyl)ethyl] amino}propyl carbamate
98	H <sub>2</sub> N-CH(OH)-CH <sub>2</sub> -CH <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{{[(1-hydroxypropyl) amino]propyl carbamate
99	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>2</sub> -(thien-2-yl)	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{{[(2-thienylmethyl) amino]propyl carbamate
100	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>4</sub> -OH	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{{[(4-hydroxybutyl) amino]propyl carbamate

101	H <sub>2</sub> N-CH(- (S) CH <sub>2</sub> -OH) -phenyl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[ (1S)-2-hydroxy-1-phenylethyl]amino] propylcarbamate
102	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-2,4-dichloro	tert-butyl (1S,2R)-1-benzyl-3-[(2,4-dichlorobenzyl)amino]-2-hydroxypropylcarbamate
103	H <sub>2</sub> N-CH(- (R) CH <sub>2</sub> -OH) -phenyl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[ (1R)-2-hydroxy-1-phenylethyl]amino] propylcarbamate
104	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-4-C(CH <sub>3</sub> ) <sub>3</sub>	tert-butyl (1S,2R)-1-benzyl-3-[(4-tert-butylbenzyl)amino]-2-hydroxypropylcarbamate
105	H <sub>2</sub> N-CH(CH <sub>3</sub> ) -phenyl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(1-phenylethyl)amino]propylcarbamate
106	H <sub>2</sub> N-(1R,2S)-2-hydroxyinden-1-yl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[ (1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]amino]propylcarbamate
107	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3,4-dimethyl	tert-butyl (1S,2R)-1-benzyl-3-[(3,4-dimethylbenzyl)amino]-2-hydroxypropylcarbamate

## EXAMPLES 108-164

Following the general procedure of EXAMPLE 4 and making non-critical variations but reacting tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3) with the C-terminal amine (VI) of Column A, the protected alcohol (VII) of Column B is obtained.

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
108	H <sub>2</sub> N-(CH <sub>2</sub> ) <sub>6</sub> -CO-O-CH <sub>3</sub>	methyl 7-[[ (2R,3S)-3-[(tert-butoxycarbonyl)amino]-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino]heptanoate
109	H <sub>2</sub> N-CH(-CH <sub>3</sub> )-CO-NH-CH <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub> r/s	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[2-(isobutylamino)-1-methyl-2-oxoethyl]amino]propylcarbamate
110	H <sub>2</sub> N-CH((S)-CH <sub>3</sub> )-CO-NH-CH <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub>	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[ (1S)-2-(isobutylamino)-1-methyl-2-oxoethyl]amino]propylcarbamate

111	$\text{H}_2\text{N}-\text{C}(-\text{CH}_3)_2-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([2-(isobutylamino)-1,1-dimethyl-2-oxoethyl]amino)propylcarbamate
112	$\text{H}_2\text{N}-\text{CH}_2-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([2-(isobutylamino)-2-oxoethyl]amino)propylcarbamate
113	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_2\text{CH}_3)-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((1S)-1-[(isobutylamino)carbonyl]propyl)amino)propylcarbamate
114	$\text{H}_2\text{N}-\text{CH}((\text{R})-\text{CH}_2\text{CH}_3)-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((1R)-1-[(isobutylamino)carbonyl]propyl)amino)propylcarbamate
115	$\text{H}_2\text{N}-\text{CH}_2-\text{phenyl}$	tert-butyl (1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate
116	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}_3$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-(ethylamino)-2-hydroxypropylcarbamate
117	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isobutylamino)propylcarbamate
118	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CONH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([3-(isobutylamino)-2-methyl-3-oxopropyl]amino)propylcarbamate
119	$\text{H}_2\text{N}-\text{CH}_2-\text{phenyl}-4-\text{N}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-([4-(dimethylamino)benzyl]amino)-2-hydroxypropylcarbamate
120	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_2-\text{phenyl})-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-3-([(1S)-1-(3,5-difluorobenzyl)-2-(isobutylamino)-2-oxoethyl]amino)-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate
121	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}(\text{CH}_3)_2)-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((1S)-1-[(isobutylamino)carbonyl]-3-methylbutyl)amino)propylcarbamate
122	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-([2-(dimethylamino)ethyl]amino)-2-

		hydroxypropylcarbamate
123	$\text{H}_2\text{N}-\text{CH}_2-(\text{pyridin-3-yl})$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-pyridinylmethyl)amino]propylcarbamate
124	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_2-\text{O}-\text{CH}_2-\text{phenyl})-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-3-[[ (1S)-1-[(benzyloxy)methyl]-2-(isobutylamino)-2-oxoethyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate
125	$\text{H}_2\text{N}-\text{C}(-\text{CH}_3)_2-\text{phenyl}$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1-methyl-1-phenylethyl)amino]propylcarbamate
126	$\text{H}_2\text{N}-\text{CH}((\text{R})-\text{CH}(\text{CH}_3)_2)-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[( (1R)-1-[(isobutylamino)carbonyl]-3-methylbutyl)amino]propylcarbamate
127	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_2-\text{CH}_2-\text{CH}_3)-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[( (1S)-1-[(isobutylamino)carbonyl]butyl)amino]propylcarbamate
128	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_2-\text{OH})-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[ (1S)-1-(hydroxymethyl)-2-(isobutylamino)-2-oxoethyl]amino]propylcarbamate
129	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{phenyl}$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-phenylethyl)amino]propylcarbamate
130	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_3)-\text{CO}-\text{NH}-\text{CH}_2-\text{phenyl}$	tert-butyl (1S,2R)-3-[[2-(benzylamino)-1-methyl-2-oxoethyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate
131	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_2-\text{CH}_3)-\text{phenyl}$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[[ (1S)-2-(benzylamino)-1-methyl-2-oxoethyl]amino]-2-hydroxypropylcarbamate
132	$\text{H}_2\text{N}-\text{CH}_2-\text{phenyl}-3-\text{OCH}_3$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
133	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{phenyl})-\text{CO}-\text{NHCH}_2\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[ (1S)-2-(isobutylamino)-2-oxo-1-



		phenylethyl]amino}propylcarbamate
134	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isopentylamino)propylcarbamate
135	$\text{H}_2\text{N}-\text{cyclohexyl}$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclohexylamino)-2-hydroxypropylcarbamate
136	$\text{H}_2\text{N}-(\text{CH}_2)_3-\text{CH}_3$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-(butylamino)-2-hydroxypropylcarbamate
137	$\text{H}_2\text{N}-(\text{CH}_2)_3-\text{O}-\text{CH}_3$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxypropyl)amino]propylcarbamate
138	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}(\text{OH})-\text{phenyl}$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-hydroxy-2-phenylethyl)amino]propylcarbamate
139	$\text{H}_2\text{N}-\text{cyclohexyl}-3,5\text{-dimethoxy}$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[[ (3R,5S)-3,5-dimethoxycyclohexyl]amino]-2-hydroxypropylcarbamate
140	$\text{H}_2\text{N}-\text{cyclohexyl}-3,5\text{-di-}(-\text{CO}-\text{OCH}_3)$	dimethyl (1R,3S)-5-({ (2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-4-phenylbutyl}amino)-1,3-cyclohexanedicarboxylate
141	$\text{H}_2\text{N}-\text{cyclohexyl}-3,5\text{-di-}(-\text{COOH})$	(1R,3S)-5-({ (2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-4-phenylbutyl}amino)-1,3-cyclohexanedicarboxylic acid
142	$\text{H}_2\text{N}-\text{CH}((\text{R})-\text{CH}_2-\text{CH}_3)-\text{phenyl}$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[ (1R)-1-phenylpropyl]amino]propylcarbamate
143	$\text{H}_2\text{N}-\text{CH}_2-\text{phenyl}-3\text{-Cl}$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-chlorobenzyl)amino]-2-hydroxypropylcarbamate
144	$\text{H}_2\text{N}-\text{CH}_2-\text{phenyl}-3\text{-OCH}_3$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
145	$\text{H}_2\text{N}-\text{CH}_2-\text{phenyl}-\text{phenyl}$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[[[1,1'-biphenyl]-3-ylmethyl]amino]-2-hydroxypropylcarbamate
146	$\text{H}_2\text{N}-\text{CH}_2-\text{phenyl}-3\text{-I}$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-

		iodobenzyl) amino] propylcarbamate
147	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3-CH <sub>3</sub>	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methylbenzyl) amino] propylcarbamate
148	H <sub>2</sub> N-CH <sub>2</sub> -CH(-CH <sub>3</sub> )-phenyl	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-phenylpropyl) amino] propylcarbamate
149	H <sub>2</sub> N-CH <sub>2</sub> -(thiazol-5-yl)	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1,3-thiazol-5-ylmethyl) amino] propylcarbamate
150	H <sub>2</sub> N-CH <sub>2</sub> -(thien-2-yl)	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-thienylmethyl) amino] propylcarbamate
151	H <sub>2</sub> N-4-methoxytetralin-1-yl	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(5-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl) amino] propylcarbamate
152	H <sub>2</sub> N-CH <sub>2</sub> -pyrazin-2-yl	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-pyrazinylmethyl) amino] propylcarbamate
153	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3,5-difluoro	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3,5-difluorobenzyl) amino]-2-hydroxypropylcarbamate
154	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3,4-methylenedioxy	tert-butyl (1S,2R)-3-[(1,3-benzodioxol-5-ylmethyl) amino]-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate
155	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3,5-dimethoxy	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3,5-dimethoxybenzyl) amino]-2-hydroxypropylcarbamate
156	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3-CF <sub>3</sub>	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl] amino] propylcarbamate
157	H <sub>2</sub> N-CH <sub>2</sub> -(furan-2-yl)	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-furylmethyl) amino]-2-hydroxypropylcarbamate
158	H <sub>2</sub> N-(7-methoxytetralin-1-yl)	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(7-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl) amino] propylcarbamate

		e
159	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3-O-CF <sub>3</sub>	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([3-(trifluoromethoxy)benzyl]amino)propylcarbamate
160	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3-F	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-fluorobenzyl)amino]-2-hydroxypropylcarbamate
161	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3-O-CH(CH <sub>3</sub> ) <sub>2</sub>	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropoxybenzyl)amino]propylcarbamate
162	H <sub>2</sub> N-CH <sub>2</sub> -phenyl-3-Br	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-bromobenzyl)amino]-2-hydroxypropylcarbamate
163	H <sub>2</sub> N-CH <sub>2</sub> -(5-methylfuran-2-yl)	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([(5-methyl-2-furyl)methyl]amino)propylcarbamate
164	H <sub>2</sub> N-(5-methoxytetralin-1-yl)	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(5-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]propylcarbamate

EXAMPLE 165 tert-Butyl-(1S, 2R)-3-azido-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (XII)

Sodium azide (0.22 g, 4 mmole) and ammonium chloride (2  
 5 eq) are added to tert-butyl (1S)-2-(3,5-difluorophenyl)-1-  
 [(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3, 0.6 g, 2 mmole).  
 The reaction is heated to 75-80 degrees C and stirred for 16  
 hours. The reaction is monitored by TLC to insure completion.  
 The solvent is removed under reduced pressure. The concentrate  
 10 is partitioned between ethyl acetate and water, the phases are  
 separated and the organic phase is washed with bicarbonate and  
 saline, dried over anhydrous sodium sulfate and concentrated to  
 give the title compound, TLC (ethyl acetate/hexane) R<sub>f</sub> = 0.45;  
 MS (MH<sup>+</sup>) = 343.

EXAMPLE 166 (2R, 3S)-3-amino-1-azido-4-(3,5-difluorophenyl)-2-butanol (XIV).

tert-Butyl-(1S, 2R)-3-azido-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (XII, EXAMPLE 165, 0.48 g, 1.41 mmole) is dissolved in dichloromethane (20 ml) to which trifluoroacetic acid (5 ml) is added. The reaction is stirred at 20-25 degrees C for 16 hours and the solvent is removed under reduced pressure with heat. Ethyl acetate is added twice and evaporated twice to give the title compound as the trifluoroacetic acid salt which is used in the next reaction without further purification; MS (MH<sup>+</sup>) = 242.

EXAMPLE 167 N<sup>1</sup>-[(1S,2R)-3-azido-1-(3,5-difluorobenzyl)-2-hydroxypropyl]5-methyl-N<sup>3</sup>,N<sup>3</sup>-dipropylisophthalamide (XV)

To (2R, 3S)-3-amino-1-azido-4-(3,5-difluorophenyl)-2-butanol (XIV, EXAMPLE 166, 0.34 g, 1.4 mmole) in dichloromethane (20 ml) is added N,N-dipropylamidoisophthalic acid (IX, 0.53 g, 2 mmole), t-butyl alcohol (0.27 g, 2 mmole) and triethylamine (0.84 ml, 6 mmole) and ethyl-1-(3-dimethylaminopropyl)carbodiimide (0.58 g, 3 mmole). The mixture is stirred at 20-25 degrees C for 16 hours. The reaction is monitored by TLC (methanol/dichloromethane, 20/80 + ethyl acetate/hexane, 50/50; R<sub>f</sub> = 0.76). When the reaction is complete as measured by TLC, the reaction mixture is partitioned between dichloromethane and water, washed with hydrochloric acid (0.5 N), bicarbonate, saline, dried over anhydrous sodium sulfate and the solvent is removed under reduced pressure with heat to produce a concentrate. The concentrate is column chromatographed on silica gel to give the title compound; MS (MH<sup>+</sup>) = 488.

EXAMPLE 168       $N^1$ -[(1S,2R)-3-amino-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl- $N^3,N^3$ -dipropylisophthalamide acetic acid salt (XVI)

5       $N^1$ -[(1S,2R)-3-azido-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl- $N^3,N^3$ -dipropylisophthalamide (XV, EXAMPLE 167, 0.3 g, 0.62 mmole) in ethyl acetate (20 ml) and acetic acid (5ml) is placed in a Parr pressure bottle. Palladium on carbon (10%, 5 g) is added and the mixture shaken under hydrogen at 50 psi for 2 hours. The mixture is filtered

10 through a diatomaceous earth and the filtrate is concentrated to give the title compound; MS ( $MH^+$ ) = 462.

EXAMPLE 169       $N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-furylmethyl)amino]-2-hydroxypropyl}-5-methyl- $N^3,N^3$ -dipropylisophthalamide (X)

15       $N^1$ -[(1S,2R)-3-amino-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl- $N^3,N^3$ -dipropylisophthalamide acetic acid salt (XVI, EXAMPLE 168, 76 mg, 0.146 mmol) is dissolved in absolute ethanol (2 mL). 3-Furaldehyde (20 microL, 0.231

20 mmol) and triethylamine (30 microL, 0.215 mmol) are added via syringe, with stirring at 20-25 degrees C. After 10 minutes, palladium on carbon 122 mg, 5 weight %) is added and the mixture placed under a hydrogen atmosphere (50 psi) and shaken for 20 minutes. The resulting mixture is then filtered through

25 diatomaceous earth, with ethanol washings. The filtrate is purified by flash chromatography (2-10% methanol/methylene chloride) to give purified title compound, MS ( $MH^+$ ) = 542.2.

EXAMPLE 169a      tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(1S)-2-(ethylamino)-1-methyl-2-oxoethyl]amino)-2-hydroxypropylcarbamate (VII)

30

Following the general procedure of EXAMPLES 4 and 14-164 and making non-critical variations and reacting tert-butyl

(1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3) with (2S)-2-amino-N-ethylpropanamide (VI), the title compound is obtained.

## 5 EXAMPLES 170-320

Following the general procedure of EXAMPLE 5 and making non-critical variations but starting with the protected alcohol (VII) of Column A, the amine (VIII) of Column B is obtained.

Column A lists the Protected Alcohols (VII) by reference  
10 to a specific Example number above.

EXA	A	Column B Amine (VIII)
170	14	(2R,3S)-3-amino-1-(ethylamino)-4-phenyl-2-butanol
171	15	(2R,3S)-3-amino-1-(benzylamino)-4-phenyl-2-butanol
172	16	(2R,3S)-3-amino-1-(isopropylamino)-4-phenyl-2-butanol
173	17	(2R,3S)-3-amino-1-[(4-methylbenzyl)amino]-4-phenyl-2-butanol
174	18	(2R,3S)-3-amino-1-{[2-(4-methoxyphenyl)ethyl]amino}-4-phenyl-2-butanol
175	19	(2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-phenyl-2-butanol
176	20	ethyl {[ (2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]amino} (phenyl) acetate
177	21	(2R,3S)-3-amino-4-phenyl-1-[(2-phenylethyl)amino]-2-butanol
178	22	(2S)-2-{[ (2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]amino}-1-(4-nitorphenyl)-1,3-propanediol
179	23	(2R,3S)-3-amino-1-[(2-chlorobenzyl)amino]-4-phenyl-2-butanol
180	24	(2R,3S)-3-amino-1-[(4-chlorobenzyl)amino]-4-phenyl-2-butanol
181	25	(2R,3S)-3-amino-1-{[2-(2-hydroxyethoxy)ethyl]amino}-4-phenyl-2-butanol
182	26	(2R,3S)-3-amino-1-(2,3-dihydro-1H-inden-1-ylamino)-4-phenyl-2-butanol
183	27	(2R,3S)-3-amino-1-[(2-hydroxypropyl)amino]-4-phenyl-2-butanol
184	28	(2R,3S)-3-amino-4-phenyl-1-[(tetrahydro-2-furanylmethyl)amino]-2-butanol
185	29	(2R,3S)-3-amino-1-[(2,2-diethoxyethyl)amino]-4-phenyl-2-butanol

186	30	(2R,3S)-3-amino-1-(butylamino)-4-phenyl-2-butanol
187	31	(2R,3S)-3-amino-1-(cyclohexylamino)-4-phenyl-2-butanol
188	32	(2R,3S)-3-amino-4-phenyl-1-[(2-pyridinylmethyl)amino]-2-butanol
189	33	(2R,3S)-3-amino-1-[(2-aminobenzyl)amino]-4-phenyl-2-butanol
190	34	(2R,3S)-3-amino-4-phenyl-1-[(3-pyridinylmethyl)amino]-2-butanol
191	35	(2R,3S)-3-amino-4-phenyl-1-[[2-(1-pyrrolidinyl)ethyl]amino]-2-butanol
192	36	(2R,3S)-3-amino-1-[(2-hydroxy-2-phenylethyl)amino]-4-phenyl-2-butanol
193	37	(2R,3S)-3-amino-1-[(3-butoxypropyl)amino]-4-phenyl-2-butanol
194	38	(2R,3S)-3-amino-1-[(3-isopropoxypropyl)amino]-4-phenyl-2-butanol
195	39	(2R,3S)-3-amino-1-(isopentylamino)-4-phenyl-2-butanol
196	40	(2R,3S)-3-amino-4-phenyl-1-[(3-phenylpropyl)amino]-2-butanol
197	41	(2R,3S)-3-amino-1-[(2-methoxyethyl)amino]-4-phenyl-2-butanol
198	42	(2R,3S)-3-amino-1-[(2-phenoxyethyl)amino]-4-phenyl-2-butanol
199	43	(2R,3S)-3-amino-4-phenyl-1-[(2-propoxyethyl)amino]-2-butanol
200	44	(2R,3S)-3-amino-1-[(3,3-dimethylbutyl)amino]-4-phenyl-2-butanol
201	45	(2R,3S)-3-amino-4-phenyl-1-[(4-phenylbutyl)amino]-2-butanol
202	46	(2R,3S)-3-amino-1-[(3-iodobenzyl)amino]-4-phenyl-2-butanol
203	47	(2R,3S)-3-amino-1-[(4-nitrobenzyl)amino]-4-phenyl-2-butanol
204	48	(2R,3S)-3-amino-1-[(3-chlorobenzyl)amino]-4-phenyl-2-butanol
205	49	(2R,3S)-3-amino-1-[[2-(4-chlorophenyl)ethyl]amino]-4-phenyl-2-butanol
206	50	(2R,3S)-3-amino-4-phenyl-1-[[2-(2-pyridinyl)ethyl]amino]-2-butanol
207	51	(2R,3S)-3-amino-4-phenyl-1-[(4-pyridinylmethyl)amino]-2-butanol
208	52	(2R,3S)-3-amino-1-[[2-(1-methyl-2-pyrrolidinyl)ethyl]amino]-4-phenyl-2-butanol
209	53	(2R,3S)-3-amino-1-[(2,3-dimethylbenzyl)amino]-4-phenyl-2-butanol
210	54	(2R,3S)-3-amino-4-phenyl-1-[[2-(trifluoromethoxy)benzyl]amino]-2-butanol

211	55	(2R,3S)-3-amino-1-[(2-chloro-6-phenoxybenzyl)amino]-4-phenyl-2-butanol
212	56	(2R,3S)-3-amino-4-phenyl-1-[[4-(trifluoromethyl)benzyl]amino]-2-butanol
213	57	(2R,3S)-3-amino-1-[(2,3-dichlorobenzyl)amino]-4-phenyl-2-butanol
214	58	(2R,3S)-3-amino-1-[(3,5-dichlorobenzyl)amino]-4-phenyl-2-butanol
215	59	(2R,3S)-3-amino-1-[(3,5-difluorobenzyl)amino]-4-phenyl-2-butanol
216	60	(2R,3S)-3-amino-4-phenyl-1-[[4-(trifluoromethoxy)benzyl]amino]-2-butanol
217	61	4-([[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]amino)methyl)benzenesulfonamide
218	62	(2R,3S)-3-amino-1-[(4-methoxybenzyl)amino]-4-phenyl-2-butanol
219	63	(2R,3S)-3-amino-1-[(4-methylbenzyl)amino]-4-phenyl-2-butanol
220	64	(2R,3S)-3-amino-4-phenyl-1-[(3,4,5-trimethoxybenzyl)amino]-2-butanol
221	65	(2R,3S)-3-amino-4-phenyl-1-[[3-(trifluoromethoxy)benzyl]amino]-2-butanol
222	66	(2R,3S)-3-amino-1-[(3,5-dimethoxybenzyl)amino]-4-phenyl-2-butanol
223	67	(2R,3S)-3-amino-1-[(2,4-dimethoxybenzyl)amino]-4-phenyl-2-butanol
224	68	(2R,3S)-3-amino-1-[[[1,1'-biphenyl]-3-ylmethyl]amino]-4-phenyl-2-butanol
225	69	(2R,3S)-3-amino-1-[(3,4-dichlorobenzyl)amino]-4-phenyl-2-butanol
226	70	(2R,3S)-3-amino-1-[(2-fluorobenzyl)amino]-4-phenyl-2-butanol
227	71	(2R,3S)-3-amino-4-phenyl-1-[[3-(trifluoromethyl)benzyl]amino]-2-butanol
228	72	(2R,3S)-3-amino-1-[(2-methylbenzyl)amino]-4-phenyl-2-butanol
229	73	(2R,3S)-3-amino-4-phenyl-1-[[[(1R)-1-phenylethyl]amino]-2-butanol
230	74	(2R,3S)-3-amino-4-phenyl-1-[[[(1S)-1-phenylethyl]amino]-2-butanol
231	75	(2R,3S)-3-amino-1-[[3,5-bis(trifluoromethyl)benzyl]amino]-4-phenyl-2-butanol
232	76	(2R,3S)-3-amino-4-phenyl-1-[[2-(trifluoromethyl)benzyl]amino]-2-butanol
233	77	(2R,3S)-3-amino-1-[[[(1S)-1-(1-naphthyl)ethyl]amino]-4-phenyl-2-butanol
234	78	(2R,3S)-3-amino-1-[[[(1R)-1-(1-naphthyl)ethyl]amino]-4-phenyl-2-butanol



235	79	4-([[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]amino)methyl)-2-methoxyphenol
236	80	4-([[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]amino)methyl)-1,2-benzenediol
237	81	(2R,3S)-3-amino-1-[(3-methoxypropyl)amino]-4-phenyl-2-butanol
238	82	(2R,3S)-3-amino-1-([(1S)-2-hydroxy-1-methylethyl]amino)-4-phenyl-2-butanol
239	83	(2R,3S)-3-amino-1-([(1R)-2-hydroxy-1-methylethyl]amino)-4-phenyl-2-butanol
240	84	(2R,3S)-3-amino-4-phenyl-1-(2-propynylamino)-2-butanol
241	85	(2R,3S)-3-amino-1-([2-(2-fluorophenyl)ethyl]amino)-4-phenyl-2-butanol
242	86	(2R,3S)-3-amino-1-([2-(3-fluorophenyl)ethyl]amino)-4-phenyl-2-butanol
243	87	(2R,3S)-3-amino-1-([2-(4-fluorophenyl)ethyl]amino)-4-phenyl-2-butanol
244	88	(2R,3S)-3-amino-1-([2-(4-bromophenyl)ethyl]amino)-4-phenyl-2-butanol
245	89	(2R,3S)-3-amino-1-([2-(3-methoxyphenyl)ethyl]amino)-4-phenyl-2-butanol
246	90	(2R,3S)-3-amino-1-([2-(2,4-dichlorophenyl)ethyl]amino)-4-phenyl-2-butanol
247	91	(2R,3S)-3-amino-1-([2-(3-chlorophenyl)ethyl]amino)-4-phenyl-2-butanol
248	92	(2R,3S)-3-amino-1-([2-(2,5-dimethoxyphenyl)ethyl]amino)-4-phenyl-2-butanol
249	93	(2R,3S)-3-amino-1-([2-(4-methylphenyl)ethyl]amino)-4-phenyl-2-butanol
250	94	(2R,3S)-3-amino-1-([(1R)-1-benzyl-2-hydroxyethyl]amino)-4-phenyl-2-butanol
251	95	(2R,3S)-3-amino-1-([3-(4-morpholinyl)propyl]amino)-4-phenyl-2-butanol
252	96	(2R,3S)-3-amino-1-(isobutylamino)-4-phenyl-2-butanol
253	97	(2R,3S)-3-amino-1-([2-(4-morpholinyl)ethyl]amino)-4-phenyl-2-butanol
254	98	(2R,3S)-3-amino-4-phenyl-1-[(2-hydroxybutyl)amino]-2-butanol
255	99	(2R,3S)-3-amino-4-phenyl-1-([2-(2-thienyl)ethyl]amino)-2-butanol
256	100	4-([[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]amino)-1-butanol
257	101	(2R,3S)-3-amino-1-([(1S)-2-hydroxy-1-phenylethyl]amino)-4-phenyl-2-butanol
258	102	(2R,3S)-3-amino-1-[(2,4-dichlorobenzyl)amino]-4-phenyl-2-butanol
259	103	(2R,3S)-3-amino-1-([(1R)-2-hydroxy-1-phenylethyl]amino)-4-phenyl-2-butanol

260	104	(2R,3S)-3-amino-1-[(4-tert-butylbenzyl)amino]-4-phenyl-2-butanol
261	105	(2R,3S)-3-amino-4-phenyl-1-[(1-phenylethyl)amino]-2-butanol
262	106	(1R,2S)-1-{[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]amino}-2,3-dihydro-1H-inden-2-ol
263	107	(2R,3S)-3-amino-1-[(3,4-dimethylbenzyl)amino]-4-phenyl-2-butanol
264	108	methyl 7-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}heptanoate
265	109	2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutylpropanamide
266	110	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutylpropanamide
267	111	2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutyl-2-methylpropanamide
268	112	2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutylacetamide
269	113	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutylbutanamide
270	114	(2R)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutylbutanamide
271	115	(2R,3S)-3-amino-1-(benzylamino)-4-(3,5-difluorophenyl)-2-butanol
272	116	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-(ethylamino)-2-butanol
273	117	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-(isobutylamino)-2-butanol
274	118	3-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutyl-2-methylpropanamide
275	119	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[4-(dimethylamino)benzyl]amino}-2-butanol
276	120	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutyl-3-phenylpropanamide
277	121	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutyl-3-methylbutanamide
278	122	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[2-(dimethylamino)ethyl]amino}-2-butanol
279	123	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[3-pyridinylmethyl]amino}-2-butanol
280	124	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(benzyloxy)-N-isobutylpropanamide
281	125	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(1-methyl-1-phenylethyl)amino]-2-butanol
282	126	(2R)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutyl-3-methylbutanamide
283	127	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutylpentanamide

284	128	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-hydroxy-N-isobutylpropanamide
285	129	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(2-phenylethyl)amino]-2-butanol
286	130	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-benzylpropanamide
287	131	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(1S)-1-phenylpropyl]amino]-2-butanol
287 a	169a	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-ethylpropanamide
288	132	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxybenzyl)amino]-2-butanol
289	133	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutyl-2-phenylethanamide
290	134	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-(isopentylamino)-2-butanol
291	135	(2R,3S)-3-amino-1-(cyclohexylamino)-4-(3,5-difluorophenyl)-2-butanol
292	136	(2R,3S)-3-amino-1-(butylamino)-4-(3,5-difluorophenyl)-2-butanol
293	137	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxypropyl)amino]-2-butanol
294	138	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(2-hydroxy-2-phenylethyl)amino]-2-butanol
295	139	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3R,5S)-3,5-dimethoxycyclohexyl]amino]-2-butanol
296	140	dimethyl (1R,3S)-5-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-1,3-cyclohexanedicarboxylate
297	141	(1R,3S)-5-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-1,3-cyclohexanedicarboxylic acid
298	142	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(1R)-1-phenylpropyl]amino]-2-butanol
299	143	(2R,3S)-3-amino-1-[(3-chlorobenzyl)amino]-4-(3,5-difluorophenyl)-2-butanol
300	144	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxybenzyl)amino]-2-butanol
301	145	(2R,3S)-3-amino-1-[[1,1'-biphenyl]-3-ylmethyl]amino]-4-(3,5-difluorophenyl)-2-butanol
302	146	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]-2-butanol
303	147	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methylbenzyl)amino]-2-butanol
304	148	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(2-phenylpropyl)amino]-2-butanol
305	149	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(1,3-thiazol-5-ylmethyl)amino]-2-butanol
306	150	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(2-thienylmethyl)amino]-2-butanol

307	151	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(5-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]-2-butanol
308	152	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(2-pyrazinylmethyl)amino]-2-butanol
309	153	(2R,3S)-3-amino-1-[(3,5-difluorobenzyl)amino]-4-(3,5-difluorophenyl)-2-butanol
310	154	(2R,3S)-3-amino-1-[(1,3-benzodioxol-5-ylmethyl)amino]-4-(3,5-difluorophenyl)-2-butanol
311	155	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3,5-dimethoxybenzyl)amino]-2-butanol
312	156	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-(trifluoromethyl)benzyl)amino]-2-butanol
313	157	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(2-furylmethyl)amino]-2-butanol
314	158	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(7-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]-2-butanol
315	159	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-(trifluoromethoxy)benzyl)amino]-2-butanol
316	160	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-fluorobenzyl)amino]-2-butanol
317	161	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-isopropoxybenzyl)amino]-2-butanol
318	162	(2R,3S)-3-amino-1-[(3-bromobenzyl)amino]-4-(3,5-difluorophenyl)-2-butanol
319	163	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(5-methyl-2-furylmethyl)amino]-2-butanol
320	164	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(5-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]-2-butanol

EXAMPLE 587  $N^1$ -{(1S,2R)-1-Benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}- $N^3,N^3$ -dipropyl-1,3,5-benzenetricarboxamide (X)

5 To a mixture of 3-(aminocarbonyl)-5-[(dipropylamino)carbonyl]benzoic acid (IX, PREPARATION 6, 0.18 g, 0.616 mmol) in dry DMF (16 mL) is added EDC (0.182 g, 0.9 mmol), HOBT (0.127 g, 0.9 mmol), triethylamine (0.062 g, 0.616 mol), and (2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-phenyl-  
 10 2-butanol (VIII, EXAMPLE 175, 0.185 g, 0.616 mmol). The mixture is stirred at 20-25 degrees C for 3 days. The mixture is partitioned between water and ethyl acetate. The phases are separated and the organic phase is washed three times with

water. The organic phase is dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography (silica gel, 75 mL; methanol/methylene chloride, 10/90) gives the title compound, IR (diffuse reflectance) 3306, 3301, 3270, 2962, 1676, 1667, 1663, 1645, 1638, 1627, 1615, 1550, 1537, 1450 and 1439  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  0.645, 0.968, 1.20, 1.43, 1.67, 2.8, 2.97, 3.38, 3.47, 3.73, 3.87, 4.31, 6.78, 6.91, 7.23, 7.72, 7.87, 8.22 and 8.43.

10 EXAMPLE 588 1- *tert*-butyl (1*S*,2*R*)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propylcarbamate (VII)

*tert*-Butyl (1*S*)-2-(3,5-difluorophenyl)-1-[(2*S*)-oxiranyl]ethylcarbamate (V, EXAMPLE 3, 1.75 g, 5.8 mmole) is mixed with isopropanol (30 ml). The reaction flask is charged with 3-iodobenzylamine (VI). The reaction mixture is heated to reflux for 45 minutes, HPLC analysis indicates complete disappearance of the epoxide (V). The reaction mixture is concentrated under reduced pressure and the residue is partitioned between ethyl acetate (150 ml) and aqueous hydrochloric acid (3%, 35 ml). The organic phase is separated and washed with aqueous hydrochloric acid (3%, 20 ml), bicarbonate, saline and dried over sodium sulfate. Concentration under reduced pressure gives the title compound, M + H = 535.

EXAMPLE 589 1-9H-fluoren-9-ylmethyl (2*R*,3*S*)-3-(3-*t*-butyloxycarbonyl)amino-4-(3,5-difluorophenyl)-2-hydroxybutyl(3'-iodobenzyl)carbamate hydrochloride (XXXIV)

1- *tert*-butyl (1*S*,2*R*)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propylcarbamate (VII, EXAMPLE 588, 2.5 g, 4.7 mmole) and triethylamine (0.72 ml, 5.1 mmole) in THF (10 ml) are mixed. The reaction is cooled to 0 degrees and treated

with Fmoc-Cl (1.2 g, 4.7 mmole) in THF (2 ml) via addition funnel. After 15 minutes HPLC indicates complete disappearance of starting material. The reaction is diluted with ethyl acetate and washed with aqueous potassium bisulfate, saturated aqueous bicarbonate, saline and dried over sodium sulfate. Concentration under reduced pressure gives crude product which is purified by flash chromatography, eluting with ethyl acetate/hexane (20/80) followed by ethyl acetate to give the title compound, M + H = 757.

10

EXAMPLE 590 1-9H-fluoren-9-ylmethyl (2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl(3-iodobenzyl)carbamate hydrochloride (XXXV)

15 1-9H-fluoren-9-ylmethyl (2R,3S)-3-(3-t-butyloxycarbonyl)amino-4-(3,5-difluorophenyl)-2-hydroxybutyl(3'-iodobenzyl)carbamate hydrochloride (XXXIV, EXAMPLE 589, 2.9 g) in hydrochloric acid/dioxane (4N, 10 ml). The mixture is stirred 1 hour then slowly poured into rapidly stirring ether (200 ml). The product is filtered and dried to give the title compound, M + H = 657.

20 EXAMPLE 591 1-9H-fluoren-9-ylmethyl (2R,3S)-4-(3,5-difluorophenyl)-2-hydroxy-3-[[5-oxo-5-(1-piperidinyl)pentanoyl]amino}butyl(3-iodobenzyl)carbamate (XXXVI)

25 HOBt (81 mg, 0.6 mmole) and EDC (105 mg, 0.55 mmole) are added to 1-carboxy-5-piperidinylglutaramide (IX, 100 mg, 0.5 mmole) in DMF (2 ml). The acid is activated 60 minutes then treated with 1-9H-fluoren-9-ylmethyl (2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl(3-iodobenzyl)carbamate hydrochloride (XXXV, EXAMPLE 590, 300 mg, 0.43 mmole) and NMM (0.19 ml, 1.72 mmole). The reaction is stirred 3 hours then concentrated under reduced pressure. The residue is

partitioned between ethyl acetate and saturated aqueous bicarbonate. The organic phases are washed with aqueous potassium bisulfate, saline, dried over sodium sulfate and finally concentrated under reduced pressure to give crude product. Purification via flash chromatography with ethyl acetate/hexane (50/50) then methanol/ethyl acetate (10/90) gives the title compound, M + H = 838.

EXAMPLE 592 1- N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-5-oxo-5-(1-piperidinyl)pentanamide trifluoroacetate (X)

1- N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-5-oxo-5-(1-piperidinyl)pentanamide trifluoroacetate (XXXVI, EXAMPLE 591, 240 mg, 0.29 mmole is dissolved in diethylamine (10%, 9 ml) in methylene chloride. The reaction is stirred at 20-25 degrees overnight. The next morning the reaction is concentrated under reduced pressure and the residue is redissolved in methylene chloride and purified by preparative reverse phase HPLC. The appropriate fractions are pooled, and concentrated under reduced pressure and partitioned between ethyl acetate and saline. The organic phase is separated and dried over sodium sulfate and concentrated to give the title compound, M + H = 614.

EXAMPLE 593 5-(Aminosulfonyl)-N<sup>1</sup>-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N<sup>3</sup>,N-dipropylisophthalamide (X)

O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 0.0928 g, 0.244 mmol) is added to a mixture of, 3-(aminosulfonyl)-5-[(dipropylamino)-carbonyl]benzoic acid (XXXIX, PREPARATION 13, 0.0800 g, 0.244 mmol) and (2R,3S)-3-amino-1-[(3-methoxybenzyl)-amino]-4-phenyl-2-butanol (VIII, EXAMPLE 175, 0.0732 g, 0.244 mmol) in dry DMF (3 mL). The mixture is stirred for 18 hours at 20-25 degrees,

and then partitioned between ethyl acetate and water. The organic phase is separated and washed with saline, dried over anhydrous sodium sulfate, filtered and concentrated. The concentrate is column chromatographed (silica gel; 5 methanol/dichloromethane, 5/95) to give the title compound, MS (ESI+) for  $C_{32}H_{42}N_4O_6S$   $m/z$   $(M+H)^+ = 611.5$ ; HRMS (FAB) calculated for  $C_{32}H_{42}N_4O_6S + H_1 = 611.2903$ , found = 611.2904.

10 EXAMPLE 620  $N^1$ -{(1S,2R)-1-Benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-ethyl- $N^3, N^3$ -dipropylisophthalamide (X)

Diethyl cyanophosphonate (0.132 mL, 0.870 mmol) is added to a mixture of 3-[(dipropylamino)carbonyl]-5-ethylbenzoic 15 acid (IX, PREPARATION 21, 0.200 g, 0.720 mmol), (2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-phenyl-2-butanol (VIII, EXAMPLE 175, 0.216 mg, 0.720 mmol), and triethylamine (0.121 mL, 0.870 mmol) in dichloromethane (3 mL). The mixture was stirred for 1 hour at 20-25 degrees C. Dichloromethane is then 20 removed under reduced pressure. The residue is partitioned between ethyl acetate and water. The organic phase is separated and is washed with saline, dried over anhydrous sodium sulfate, filtered and concentrated. The concentrate is column chromatographed (silica gel; methanol/dichloromethane, 25 5/95) to give the title compound, MS (ESI+) for  $C_{34}H_{45}N_3O_4$   $m/z$   $(M+H)^+ = 560.4$ ; HRMS (FAB) calculated for  $C_{34}H_{45}N_3O_4 + H = 560.3488$ , found = 560.3487.

30 EXAMPLE 629  $N$ -{(1S,2R)-1-Benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[butyryl(propyl)amino]-5-methylbenzamide (X)

Following the procedure of EXAMPLE 570 and making non-critical variations, diethyl cyanophosphonate (0.0760 mL, 0.550 mmol) is added to a mixture of 3-[butyryl(propyl)amino]-5-



methylbenzoic acid (IX, 0.120 g, 0.460 mmol), (2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-phenyl-2-butanol (VIII, 0.137 g, 0.460 mmol), and triethylamine (0.0760 mL, 0.550 mmol) in dichloromethane (5 mL). The mixture is stirred for 1 hour at  
5 20-25 degrees C. Dichloromethane is then removed under reduced pressure. The residue is partitioned between ethyl acetate and water. The organic is separated, is washed with saline, dried over anhydrous sodium sulfate, filtered and concentrated. The concentrate is column chromatographed (silica gel;  
10 methanol/dichloromethane, 5/95) to give the title compound, NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.09, 4.15, 3.80, 3.79, 3.60, 3.02, 2.84, 2.36, 1.94, 1.56, 1.49, 0.87 and 0.81;. MS (ESI+) for C<sub>33</sub>H<sub>43</sub>N<sub>3</sub>O<sub>4</sub>  $m/z$  (M+H)<sup>+</sup> = 546.3; HRMS (FAB) calculated for C<sub>33</sub>H<sub>43</sub>N<sub>3</sub>O<sub>4</sub>+H = 546.3331, found = 546.3331.

15

EXAMPLE 631 N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-1-propyl-1H-indole-6-carboxamide (X)

20 EXAMPLE 682 N<sup>1</sup>-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-ethynyl-N<sup>3</sup>,N<sup>3</sup>-dipropylisophthalamide, (M+H)<sup>+</sup> = 590

EXAMPLE 739 N<sup>1</sup>-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-5-(cyanomethyl)-  
25 N<sup>3</sup>,N<sup>3</sup>-dipropylisophthalamide (X)

Step 1. A mixture of diethyl 1,3,5-benzenetricarboxylate (5.2 g) and borane methylsulfide complex (6.1 g) is stirred in THF (150 mL) at 20-25 degrees C overnight. The mixture is then  
30 treated with methanol, concentrated to dryness, and chroumatographed (silica gel) to give diethyl 5-(hydroxymethyl)isophthalate. Diethyl 5-(hydroxymethyl)isophthalate (3.4 g) is hydroyzed in ethanol and water with lithium hydroxide monohydrate (0.57 g) at 20-25

degrees C for 3.5 hours at which time the solvents are removed under reduced pressure. Water (100 mL) is added and the mixture is acidified to pH = 4 with concentrated hydrochloric acid. The mixture is extracted with ethyl acetate and dried  
5 over magnesium sulfate, filtered, and concentrated to give 3-(ethoxycarbonyl)-5-(hydroxymethyl)benzoic acid, high resolution MS MH+ = 225.0769. 3-(Ethoxycarbonyl)-5-(hydroxymethyl)benzoic acid (2.3 g), EDC (3.0 g), 1-HOBT (2.1 g), diisopropylethylamine (2.7 mL), dipropyl amine (2.8 mL),  
10 and DMF (50 mL) are stirred at 20-25 degrees C overnight. The mixture is then partitioned between ethyl acetate, water, and saline. The organic phase is separated and dried over magnesium sulfate, filtered, and concentrated. Chromatography (silica gel) gives ethyl 3-[(dipropylamino)carbonyl]-5-(hydroxymethyl)benzoate, NMR (CDCl<sub>3</sub>)  $\delta$  0.77, 1.0, 1.4, 1.6,  
15 1.7, 3.2, 3.5, 4.4, 4.8, 7.6, 8.0 and 8.1.

Step 2. A mixture of ethyl 3-[(dipropylamino)carbonyl]-5-(hydroxymethyl)benzoate (1.5 g) and phosphorous tribromide (0.95 mL) is stirred in dichloromethane (10 mL) and heated at  
20 50 degrees C for 4 hours and then cooled and partitioned between dichloromethane and water. The organic phase is separated and washed with aqueous sodium bicarbonate and then dried over magnesium sulfate and taken to dryness to give ethyl 3-(bromomethyl)-5-[(dipropylamino)carbonyl]benzoate, high  
25 resolution MS MH+ = 370.1020. Ethyl 3-(bromomethyl)-5-[(dipropylamino)carbonyl]benzoate (1.4 g) and sodium cyanide (0.2 g) are stirred in dry DMSO (25 mL) at 20-25 degrees C for 3.5 hours and the mixture is then partitioned between ethyl acetate, water and saline. The organic layer is separated and  
30 dried over magnesium sulfate and taken to dryness under reduced pressure to give ethyl 3-(cyanomethyl)-5-[(dipropylamino)carbonyl]benzoate. Ethyl 3-(cyanomethyl)-5-[(dipropylamino)carbonyl]benzoate (0.6 g) is hydrolyzed with lithium hydroxide monohydrate (0.1 g) in ethanol and water at

20-25 degrees C overnight and then added to water (50 mL). The pH is adjusted to 4 using concentrated hydrochloric acid and the mixture is partitioned between ethyl acetate, water, and saline. The organic phase is separated and dried over magnesium sulfate and taken to dryness under reduced pressure to give 3-(cyanomethyl)-5-[(dipropylamino)carbonyl]benzoic acid, MS M+H = 287.2.

Step 3. A mixture of 3-(cyanomethyl)-5-[(dipropylamino)carbonyl]benzoic acid (IX, 0.13 g), (2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-phenyl-2-butanol (VIII, 0.14 g), HATU (0.17 g), and dichloromethane (10 mL) is stirred at 40 degrees C overnight. After cooling, the mixture is washed with water and the organic phase is separated and dried over magnesium sulfate and taken to dryness under reduced pressure. Chromatography (silica gel) gives the title compound, M + H = 571.2

EXAMPLE 740  $N^1$ -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-(hydroxymethyl)- $N^3,N^3$ -dipropylisophthalamide (X)

Following the procedure of CHART P and EXAMPLE 739 and making non-critical variations but using 3-[(dipropylamino)carbonyl]-5-(hydroxymethyl)benzoic acid (IX) and (2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-phenyl-2-butanol (VIII), the title compound is obtained, HRMS (FAB) = 615.3571.

EXAMPLE 741  $N^1$ -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-ethynyl- $N^3,N^3$ -dipropylisophthalamide (X)

Step 1: A mixture of methyl 3-bromo-5-[(dipropylamino)carbonyl]benzoate (XXI, 200 mg, 0.58 mmol),  $PdCl_2(Ph_3P)_2$  (16 mg, 0.03 mol %) and copper (I) iodide (6 mg, 0.05 mol %) in triethylamine (1.2 mL) is heated to reflux.

(Trimethylsilyl) acetylene (100 microliter, 0.7 mmol) is added, and the mixture stirred for 3 hours, cooled to 20-25 degrees, diluted with water (20 mL), and extracted with chloroform (3 x 15 mL). The combined organic extracts are washed with saline  
5 (20 mL), dried over sodium sulfate and concentrated under reduced pressure to give methyl 3-[(dipropylamino)carbonyl]-5-ethynylbenzoate (XXXII, 185.5 mg), NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.95, 7.75, 7.43, 3.74, 3.25, 2.95, 1.49, 1.34, 0.79, 0.56 and 0.06.

10 Step 2: To a stirred mixture of the protected methyl 3-[(dipropylamino)carbonyl]-5-ethynylbenzoate (XXXII, Step 1, 185.3 mg, 0.49 mmol) in methanol (2.5 mL) is added a mixture of potassium hydroxide (2.9 mL of a 1 M mixture in water, 2.9 mmol). The reaction mixture is stirred for 4 hours diluted with  
15 chloroform (40 mL), the phases are separated and the organic phase is concentrated under reduced pressure to give 3-[(dipropylamino)carbonyl]-5-ethynylbenzoic acid, NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  8.22, 8.05, 7.71, 3.48, 3.17, 3.16, 1.71, 1.55, 1.00 and 0.78.

20 Step 3: To a stirred mixture of 3-[(dipropylamino)carbonyl]-5-ethynylbenzoic acid (70 mg, 0.24 mmol) in DMF (2.5 mL) is added (2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-phenyl-2-butanol dihydrochloride (VIII, 81 mg, 0.24 mmol), HOBt (36 mg, 0.26 mmol) and  
25 diisopropylethylamine (170 microliter, 0.96 mmol). To this reaction mixture is added EDC (51mg, 0.26 mmol) and the reaction mixture is stirred overnight. The reaction mixture is diluted with ethyl acetate (30 mL), washed with water (3 x 50 mL), hydrochloric acid (1 N, 30 mL), saturated sodium  
30 bicarbonate (30 mL), saline (30 mL), dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (silica, ethyl acetate to methanol/chloroform, 1/10) gives the title compound, IR (KBr): 3276, 2956, 2921, 1610, 1450 and 1264 cm<sup>-1</sup>; ESI-MS (m/z) [M + H]<sup>+</sup> = 556.

EXAMPLE 742  $N^1$ -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}- $N^3,N^3$ -dipropyl-5-prop-1-ynylisophthalamide (X)

5       Following the general procedure of EXAMPLE 741 and making non-critical variations but using propyne in place of (trimethylsilyl) acetylene and using (2R,3S)-3-amino-1-[(3-iodobenzyl)amino]-4-phenyl-2-butanol dihydrochloride (VIII) in place of (2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-phenyl-2-  
10 butanol dihydrochloride (VIII), the title compound is obtained, IR (ATR): 3305, 2930, 2872, 1613 and 1537  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ )  $[M+H]^+ = 666$ .

EXAMPLE 743  $N^1$ -{(1S,2R)-1-benzyl-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl}-5-ethynyl-  
15  $N^3,N^3$ -dipropylisophthalamide (X)

Step 1: A mixture of tert-butyl (1S)-1-[(2S)-oxiranyl]-2-phenylethylcarbamate (V, 2.3 g, 8.7 mmol) and 3-(trifluoromethyl)benzylamine (VI, 1.9 mL, 13.1 mmol) in 2-  
20 propanol (70 mL) is heated at reflux for 4 hours. The reaction mixture is cooled to 20-25 degrees and concentrated under reduced pressure to give tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propylcarbamate (VII, 3.1 g) as a solid, ESI-MS ( $m/z$ )  $[M + H]^+ = 439$ .

25       Step 2: A mixture of tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propylcarbamate (VII, step 1, 2.5 g, 5.7 mmol) and hydrochloric acid (29 mL of a 4.0 M mixture in dioxane, 114 mmol) is stirred at 20-25 degrees. A precipitate forms and is collected by filtration,  
30 washed with ether, and dried under reduced pressure to give (2R,3S)-3-amino-4-phenyl-1-[[3-(trifluoromethyl)benzyl]amino]-2-butanol dihydrochloride (VIII, 2.13 g), ESI-MS ( $m/z$ )  $[M + H]^+ = 339$ .

Step 3: A mixture of 3-[(dipropylamino)carbonyl]-5-ethynylbenzoic acid (IX, 231 mg, 0.8 mmol), (2R,3S)-3-amino-4-phenyl-1-[[3-(trifluoromethyl)benzyl]amino]-2-butanol dihydrochloride (VIII, Step 2, 493.5 mg, 1.2 mmol) HOBt (162 mg, 1.2 mmol), and diisopropylethylamine (832 Micro Liter, 4.8 mmol) is stirred in methylene chloride (4 mL) for 15 minutes EDC (206 mg, 1.2 mmol) is added and the reaction mixture is stirred overnight. The reaction mixture is diluted with water, and extracted with methylene chloride (3 x 25 mL). The organic phase is washed with hydrochloric acid (1N, 25 mL), saturated sodium bicarbonate (25 mL), saline dried over sodium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (silica, 100% ethyl acetate to methanol/chloroform, 1/9) gives title compound, IR (ATR): 3302, 2963, 2932 and 1615  $\text{cm}^{-1}$ ; MS (m/z)  $[M + H]^+ = 549$ .

EXAMPLE 744  $N^1$ -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-5-ethynyl- $N^3,N^3$ -dipropylisophthalamide (X)

Following the general procedure of EXAMPLE 744 and making non-critical variations but using 3-iodobenzylamine hydrochloride salt (VI), the title compound is obtained, IR (ATR) 3295, 2960, 2927 and 1616  $\text{cm}^{-1}$ , APCI-MS (m/z)  $[M + H]^+ = 652$ .

EXAMPLE 745  $N^1$ -{(1S,2R)-1-benzyl-3-[(3-fluorobenzyl)amino]-2-hydroxypropyl}-5-ethynyl- $N^3,N^3$ -dipropylisophthalamide (X)

Following the general procedure of EXAMPLE 744 and making non-critical variations but using 3-fluorobenzylamine (VI), the title compound is obtained, IR (ATR): 3217, 2961, 2918 and 1615  $\text{cm}^{-1}$ ; APCI-MS (m/z)  $[M + H]^+ = 544$ .

EXAMPLE 746      $N^1$ -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}- $N^3,N^3$ -dipropyl-5-(8-quinolinyl)isophthalamide (X)

Step 1: A mixture of methyl-3-bromo-5-  
5 [(dipropylamino)carbonyl]benzoate (XLVIII, 200 mg, 0.58 mmol),  
8-quinolineboronic acid (200.6 mg, 1.2 mmol), sodium carbonate  
(870 Micro Liter of a 2 M mixture in water, 1.74 mmol) in  
toluene (6 mL) is degassed under reduced pressure for 15  
minutes and purged with argon. Palladium  
10 tetrakis(triphenylphosphine) (139 mg, 0.12 mmol) is added and  
the reaction mixture is degassed under reduced pressure for 15  
minutes and purged with argon. The reaction mixture is heated  
at reflux overnight, cooled to 20-25 degrees C and diluted with  
chloroform. The organic phase is separated and washed with  
15 water (3 x 50 mL), and saline, dried over sodium sulfate and  
concentrated under reduced pressure. Purification by flash  
column chromatography (silica, ethyl acetate/hexanes, 1.3/1)  
gives methyl 3-[(dipropylamino)carbonyl]-5-(8-  
quinolinyl)benzoate (XLIX, 176 mg), NMR (300 MHz,  $CDCl_3$ ): delta  
20 8.91, 8.42, 8.21, 8.09, 7.95, 7.86, 7.77, 7.64, 3.94, 3.49,  
3.34, 1.64, 0.99 and 0.84.

Step 2: To a mixture of methyl 3-  
[(dipropylamino)carbonyl]-5-(8-quinolinyl)benzoate (XLIX, step  
1, 175.5 mg, 0.45 mmol) in methanol (2 mL) is added lithium  
25 hydroxide (32.3 mg, 1.4 mmol) and water (500 microliter).  
After stirring overnight, the reaction mixture is partitioned  
between ethyl acetate (10 mL) and water (10 mL). The aqueous  
phase is separated and acidified with hydrochloric acid (1N),  
and extracted with chloroform (3 x 40 mL). The organic phase  
30 is washed with saline, dried (sodium sulfate) and concentrated  
under reduced pressure to give 3-[(dipropylamino)carbonyl]-5-  
(8-quinolinyl)benzoic acid (IX - L, 130 mg), NMR (300 MHz,  
 $CD_3OD$ )  $\delta$  8.84, 8.39, 8.35, 8.05, 7.96, 7.90, 7.87, 7.79, 7.68,  
3.50, 3.37, 1.76-1.61, 0.99 and 0.84.

Step 3: A mixture of 3-[(dipropylamino)carbonyl]-5-(8-quinolinyl)benzoic acid (IX - L, Step 2, 130 mg, 0.35 mmol), (2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-phenyl-2-butanol dihydrochloride (VIII, 117 mg, 0.35 mmol), HOBt (70 mg, 0.52 mmol) and diisopropylethylamine (241 microliter, 1.4 mmol) in methylene chloride (2 mL) is stirred for 15 minutes. EDC (89 mg, 0.52 mmol) is added and the reaction mixture is stirred overnight. The reaction mixture is diluted with water and extracted with methylene chloride (3 x 25 mL). The organic phase is washed with hydrochloric acid (1N, 25 mL), saturated sodium bicarbonate (25 mL), saline, dried (sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica; methanol/chloroform, 1/9) gives the title compound, IR (NaCl): 3301, 2916, 2365 and 1613  $\text{cm}^{-1}$ ; APCI-MS ( $m/z$ ) [ $M + H$ ] $^{+}$  = 659.

EXAMPLE 747      $\text{N}^3$ -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-4'-methoxy- $\text{N}^5, \text{N}^5$ -dipropyl[1,1'-biphenyl]-3,5-dicarboxamide hydrochloride (X)

Step 1: A mixture of 4-methoxyphenyl boronic acid (463 mg, 3.05 mmol), 3-bromo-5-[(dipropylamino)carbonyl]benzoic acid (XLVIII, 1.02 g, 3.05 mmol), and potassium phosphate (1.29 g, 6.10 mmol) in 1,2-dimethoxyethane (10 mL) and water (5 mL) is degassed with argon for 15 minutes. Bis(triphenylphosphine)palladium (II) chloride (21 mg, 0.03 mmol) is added, the reaction mixture is degassed again with argon, and heated at 85 degrees C overnight. The reaction mixture is cooled to 20-25 degrees C, and passed through a plug of diatomaceous earth.

The filtrate is acidified to pH = 4 with hydrochloric acid (1N) and extracted with ethyl acetate. The organic phase is washed with water and saline and dried (magnesium sulfate). The product is purified by flash column chromatography (silica



gel; ethyl acetate/acetic acid, 99/1) to give 5-[(dipropylamino)carbonyl]-4'-methoxy[1,1'-biphenyl]-3-carboxylic acid (IX - L, 667 mg), ESI-MS ( $m/z$ )  $[M + H]^+ = 356$ .

Step 2: A mixture of 5-[(dipropylamino)carbonyl]-4'-methoxy[1,1'-biphenyl]-3-carboxylic acid (IX - L, step 1, 316 mg, 0.89 mmol), (2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-phenyl-2-butanol dihydrochloride (VIII, 332 mg, 0.89 mmol), HOBt (181 mg, 1.34 mmol), and *N*-methylmorpholine (0.37 g, 3.56 mmol) in methylene chloride (8 mL) and dimethylformamide (2 mL) is stirred at 20-25 degrees for 15 minutes. EDC (257 mg, 1.34 mmol) is added and the reaction mixture is stirred for 4.5 hours. The reaction mixture is partitioned between methylene chloride and water. The organic phase is washed with hydrochloric acid (1N), water, and saline, dried (magnesium sulfate), and concentrated. The concentrate is dissolved in a minimum of methanol, treated with hydrochloric acid (3 mL of a 1.0 M mixture in ether, 3 mmol), and stirred for 10 minutes. More ether is added to precipitate the rest of the product. The precipitate is collected by filtration and dried in the vacuum oven at 50 degrees C to give the title compound, mp = 205-209 degrees C; IR (ATR): 2964 and 1649  $\text{cm}^{-1}$ ; APCI-MS ( $m/z$ )  $[M + H]^+ = 638$ .

EXAMPLE 748  $\text{N}^3$ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}- $\text{N}^5$ , $\text{N}^5$ -dipropyl[1,1'-biphenyl]-3,5-dicarboxamide hydrochloride (X)

Step 1: A mixture of tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, 500 mg, 1.67 mmol) and 3-methoxybenzylamine (VI, 0.34g, 2.51 mmol) in 2-propanol (3 mL) is heated at reflux overnight, allowed to cool to 20-25 degrees C, and concentrated under reduced pressure. The residue is crystallized from ethyl acetate/hexanes and collected by filtration to afford tert-

butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (VII, 575 mg) as a solid: ESI-MS ( $m/z$ ): 437  $[M + H]^+$ .

Step 2: A mixture of tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (VII, Step 1, 535 mg, 1.23 mmol) in methanol (2 mL) is treated with hydrochloric acid (3.2 mL of a 1.0 M mixture in ether, 3.2 mmol), and stirred at 20-25 degrees C for 30 minutes. Ether is added until a precipitate formed. The precipitate is collected by filtration is (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxybenzyl)amino]-2-butanol dihydrochloride (VIII).

Step 3: A mixture of 5-[(dipropylamino)carbonyl][1,1'-biphenyl]-3-carboxylic acid (IX, 188 mg, 0.56 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxybenzyl)amino]-2-butanol dihydrochloride (VIII, Step 2, 230 mg, 0.56 mmol), HOBt (114 mg, 0.84 mmol), and N-methylmorpholine (0.23 g, 2.24 mmol) in methylene chloride (6 mL) and dimethylformamide (1 mL) is stirred at 20-25 degrees C for 15 minutes. EDC (161 mg, 0.84 mmol) is added and the reaction mixture is stirred at 20-25 degrees C overnight. The reaction mixture is washed with water, 1 N hydrochloric acid, water, and saline, dried (sodium sulfate), and concentrated under reduced pressure to give the title compound, mp 230-233 degrees C; IR (ATR): 2965, 1651, 1596 and 1267  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ )  $[M + H]^+ = 644$ .

EXAMPLE 749  $N^3$ -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}- $N^5$ , $N^5$ -dipropyl[1,1'-biphenyl]-3,5-dicarboxamide hydrochloride (X)

30

Following the general procedure of EXAMPLE 748 and making non-critical variations but using (2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-phenyl-2-butanol dihydrochloride (VIII) in place of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-

methoxybenzyl)amino]-2-butanol dihydrochloride (VIII), the title compound is obtained, mp = 214-219 degrees C; IR (KBr): 3227, 2961, 1632 and 1605  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ )  $[M + H]^+ = 608$ .

EXAMPLE 750  $\text{N}^3$ -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-4'-[(dimethylamino)sulfonyl]- $\text{N}^5$ , $\text{N}^5$ -dipropyl-1,1'-biphenyl-3,5-dicarboxamide (X)

Step 1: A flask is charged with 1,1'-bis(diphenylphosphino)ferrocene- dichloropalladium 1:1 complex (37 mg, 0.05 mmol), potassium acetate (492 mg, 4.5 mmol) and bis(pinacolato)diboron (408 mg, 1.6 mmol) and is degassed under reduced pressure for 15 min and purged with argon. To this mixture is added a mixture of methyl 3-bromo-5-[(dipropylamino)carbonyl]benzoate (XXI, 500 mg, 1.5 mmol) in anhydrous dimethyl sulfoxide (9 mL) and the reaction mixture is stirred at 80 degrees C for 4 hours. The reaction mixture is cooled to 20-25 degrees C, diluted with toluene (50 mL), washed with water (3 x 150 mL), saline, dried (magnesium sulfate), and concentrated under reduced pressure to give methyl 3-[(dipropylamino)carbonyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate, ESI-MS ( $m/z$ )  $[M + H]^+ = 390$ .

Step 2: A mixture of methyl 3-[(dipropylamino)carbonyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (Step 1, 534 mg, 1.4 mmol), 4-bromobenzenedimethyl-sulfonamide (363 mg, 1.4 mmol), and sodium carbonate (2 mL of a 2 M mixture in water, 4.1 mmol) in toluene (10 mL) is degassed under reduced pressure for 15 minutes and then purged with argon. Palladium tetrakis(triphenylphosphine) (40 mg, 0.025 mmol) is added and the reaction mixture is degassed under reduced pressure for 15 minutes and then purged with argon. The reaction mixture is heated at reflux for 4 hours, cooled to 20-25 degrees C, filtered through a plug of diatomaceous earth and sodium sulfate, and the filtrate is concentrated under reduced pressure. Purification by flash column chromatography (silica;

ethyl acetate/hexanes, 1/1) gives methyl 4'-  
[(dimethylamino)sulfonyl]-5-[(dipropylamino)carbonyl][1,1'-  
biphenyl]-3-carboxylate (XXXVIII), ESI-MS ( $m/z$ )  $[M + H]^+ = 447$ .

Step 3: A mixture of methyl 4'-[(dimethylamino)sulfonyl]-  
5-[(dipropylamino)carbonyl][1,1'-biphenyl]-3-carboxylate  
(XXXVIII, step 2, 555 mg, 1.24 mmol) in methanol (6 mL) and  
sodium hydroxide (2 mL of a 6.0 M mixture in water, 12 mmol)  
is stirred at 20-25 degrees C for 4 hours. The reaction  
mixture is partitioned between ethyl acetate (40 mL) and water  
10 (40 mL). The aqueous phase is acidified to pH = 4 with  
hydrochloric acid (1N), extracted with ether (3 x 100 mL), and  
the combined organic phases are concentrated under reduced  
pressure to give methyl 4'-[(dimethylamino)sulfonyl]-5-  
[(dipropylamino)carbonyl][1,1'-biphenyl]-3-carboxylic acid (IX  
15 - XXXIX), NMR (300 MHz,  $CDCl_3$ ):  $\delta$  8.37, 8.12, 7.89, 7.80, 3.51,  
3.22, 2.76, 1.74, 1.59, 1.02 and 0.79.

Step 4: A mixture of the acid (IX - XXXIX, Step 3, 150 mg,  
0.35 mmol), (2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-  
phenyl-2-butanol dihydrochloride (VIII, 129 mg, 0.35 mmol) HOBT  
20 (47 mg, 0.35 mmol), and *N*-methyilmorpholine (122  $\mu$ L, 1.1 mmol)  
is stirred in methylene chloride (4 mL) for 15 minutes EDC (107  
mg, 0.62 mmol) is added and the reaction mixture is stirred  
overnight. The reaction mixture is diluted with water, and  
extracted with methylene chloride (3 x 25 mL). The organic  
25 phase is washed with hydrochloric acid (1N, 25 mL), saturated  
sodium bicarbonate (25 mL), saline, dried (sodium sulfate), and  
concentrated under reduced pressure. Purification by flash  
column chromatography (silica; 100% ethyl acetate to  
methanol/chloroform, 1/9) gives the title compound, IR (ATR):  
30 2932, 2837 and 1593  $cm^{-1}$ ; APCI-MS ( $m/z$ )  $[M + H]^+ = 715$ .

EXAMPLE 751  $N^3$ -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-  
iodobenzyl)amino]propyl}-4'-  
[(dimethylamino)sulfonyl]- $N^5,N^5$ -dipropyl-1,1'-

biphenyl-3,5-dicarboxamide (X)

Following the general procedure of EXAMPLE 750 and making non-critical variations but using 2R,3S)-3-amino-1-[(3-iodobenzyl)amino]-4-phenyl-2-butanol dihydrochloride (VIII),  
5 the title compound is obtained, IR (ATR): 3303, 2930, 2872 and 1614  $\text{cm}^{-1}$ ; APCI-MS ( $m/z$ )  $[M + H]^+ = 811$ .

EXAMPLE 752  $N^1$ -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}- $N^3,N^3$ -dipropyl-5-(3-thienyl)isophthalamide hydrochloride (X)  
10

Step 1: To an ice-cold mixture of methyl 3-amino-5-[(dipropylamino)carbonyl]benzoate (XLVIII, 1.0 g, 3.60 mmol) in aqueous hydrogen tetrafluoroborate (48% wt. in  $\text{H}_2\text{O}$ , 12.9 mmol) is added a cold mixture of aqueous sodium nitrite (0.25 g, 3.60  
15 mmol) dropwise. The mixture is stirred for 10 min and then extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a diazonium salt which is used without further purification, NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  9.26,  
20 8.86, 8.71, 4.03, 3.50, 3.22, 1.75, 1.60, 1.01 and 0.79.

Step 2: To a mixture of thiophene-3-boronic acid (1.0 g, 7.82 mmol) in methanol is added a concentrated aqueous mixture of potassium hydrogen difluoride (2.01 g, 25.8 mmol) dropwise. The reaction mixture is stirred  
25 for 10 minutes and concentrated under reduced pressure. The resulting solid is extracted with acetone and concentrated under reduced pressure gives crude material, which is recrystallized from acetone/ether to give potassium trifluoro(3-thienyl)borate salt, ESI-MS ( $m/z$ )  $[M + H]^+ = 151$ .

30 Step 3: A mixture of potassium trifluoro(3-thienyl)borate salt (step 2, 0.69 g, 1.82 mmol), diazonium salt from (XLVIII, step 1, 0.42 g, 2.19 mmol), and lead acetate (0.02 g, 0.09 mmol) in the dark is purged with argon for 15 minutes. Dioxane (8 mL) is added and the reaction mixture is degassed with argon

and stirred at 20-25 degrees C overnight. The reaction mixture is diluted with ether, washed with saline, dried over magnesium sulfate and concentrated under reduced pressure to give methyl 3-[(dipropylamino)carbonyl]-5-(3-thienyl)benzoate (XLIX) which is purified by flash chromatography (silica; ethyl acetate/hexanes, 1/1), ESI-MS ( $m/z$ )  $[M + H]^+ = 346$ .

Step 4: A mixture of methyl 3-[(dipropylamino)carbonyl]-5-(3-thienyl)benzoate (XLIX, step 3, 0.31 g, 0.88 mmol) in THF/methanol/sodium hydroxide (3/1/1, 5 mL) is stirred at 40 degrees C for 2 hours. The reaction is cooled to 20-25 degrees C, diluted with water and extracted with ethyl acetate. The aqueous phase is acidified to pH = 4 and extracted with ethyl acetate. The organic phase is washed with water and saline, dried over magnesium sulfate and concentrated under reduced pressure to give 3-[(dipropylamino)carbonyl]-5-(3-thienyl)benzoic acid (IX - L), ESI-MS ( $m/z$ )  $[M + H]^+ = 332$ .

Step 5: A mixture of 3-[(dipropylamino)carbonyl]-5-(3-thienyl)benzoic acid (IX - L, step 4, 0.26 g, 0.79 mmol), (2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-phenyl-2-butanol dihydrochloride (VIII, 0.26 g, 0.71 mmol), HOBt (0.16 g, 1.18 mmol), and triethylamine (0.44 mL, 3.15 mmol) in DMF (4 mL) is stirred at 20-25 degrees C for 10 minutes EDC (0.23 g, 1.18 mmol) is added and the reaction mixture is stirred for 4 hours. The reaction mixture is diluted with water and extracted with ethyl acetate. The organic phase is washed with hydrochloric acid (1 N), water, and saline, dried over magnesium sulfate and concentrated under reduced pressure. Recrystallization (methylene chloride/hexanes, 1/1) gives the title compound, mp = 199-201 degrees C; IR (KBr): 3278, 2961, 2874 and 2837  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ )  $[M + H]^+ = 614$ .

EXAMPLE 753 N-[(1R,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-methyl-5-pentanoylbenzamide (X)

Step 1: To an ice-cold, stirred mixture of oxalyl chloride (733 mg, 5.77 mmol) in methylene chloride (5 mL) is added 3 drops of dimethylformamide. After 10 minutes 3-(methoxycarbonyl)-5-methylbenzoic acid (LXXIII, 560 mg, 2.89 mmol) is added. The reaction mixture is stirred for 1 hour and concentrated under reduced pressure to provide an acid chloride (LXXIV), which is used without further purification.

Step 2: To a -78 degrees C, stirred mixture of acid halide (LXXIV, step 1, 612 mg, 2.89 mmol) and copper (I) bromide (415 mg, 2.89 mmol) in tetrahydrofuran (5 mL) is added butyl magnesium chloride (1.44 mL of a 2.0 M mixture in tetrahydrofuran, 2.89 mmol). The reaction mixture is warmed to 20-25 degrees C, quenched by addition of saturated ammonium chloride, and diluted with ether. The organic phase is separated, washed with saline, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica; hexanes/ethyl acetate, 6.5/1) gives methyl 3-methyl-5-pentanoylbenzoate (LXXVI), NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  8.43, 8.05, 3.96, 3.01, 1.77, 1.55 and 1.22.

Step 3: A mixture of methyl 3-methyl-5-pentanoylbenzoate (LXXVI, step 2, 133 mg, 0.605 mmol) in methanol (1 mL) is stirred with tetrahydrofuran/methanol/sodium hydroxide (2 N) (3/1/1, 3 mL) for 3 days. The reaction mixture is diluted with ethyl acetate and washed with water. The aqueous phase is separated and acidified with hydrochloric acid (1 N) and extracted with methylene chloride. The organic phase is dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 3-methyl-5-pentanoylbenzoic acid (IX - LXXVII), NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  8.44, 8.03, 3.10, 2.33, 1.78, 1.64 and 1.34.

Step 4: To a mixture of 3-methyl-5-pentanoylbenzoic acid (IX - LXXVII, 112 mg, 0.589 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxybenzyl)amino]-2-butanol

dihydrochloride (VIII, 239 mg, 0.589 mmol), HOBt (80 mg, 0.589 mmol), and *N*-methyilmorpholine (250 mg, 2.47 mmol) in methylene chloride (3 mL) is added EDC (203 mg, 1.06 mmol). The reaction mixture is stirred overnight and then partitioned between ethyl acetate and water. The organic phase is washed with hydrochloric acid (1 N), saturated sodium bicarbonate, saline, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica; methylene chloride/methanol, 12/1) gives the title compound, IR (ATR): 3297, 2957, 1687 and 1628  $\text{cm}^{-1}$ ; APCI-MS ( $m/z$ )  $[M + H]^+ = 539$ .

EXAMPLE 754  $\text{N}^1$ -(4-hydroxybutyl)- $\text{N}^3$ -{(1*S*)-2-hydroxy-1-(4-hydroxybenzyl)-3-[(3-methoxybenzyl)amino]propyl}-5-methyl- $\text{N}^1$ -propylisophthalamide (X)

Step 1: To a mixture of methyl (2*S*)-3-[4-(benzyloxy)phenyl]-2-(tert-butoxycarbonyl)aminopropanoate (1.79 g, 4.65 mmol) in a THF/methanol/water (1/2/1, 16 mL) is added lithium hydroxide (340 mg, 13.9 mmol) and the mixture stirred at 20-25 degrees C for 12 hours. The mixture is quenched with citric acid (10%). The resulting mixture is extracted with ethyl acetate (3 x 15 mL). The combined organic extracts are washed three times with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give (2*S*)-3-[4-(benzyloxy)phenyl]-2-[(tert-butoxycarbonyl)amino]propanoic acid which is carried on without purification. To a -78 degrees C, stirred mixture of (2*S*)-3-[4-(benzyloxy)phenyl]-2-[(tert-butoxycarbonyl)amino]propanoic acid (10.0 g, 27.0 mmol) in THF (200 mL) is added NMM (3.20 mL, 29.0 mmol) and isobutyl chloroformate (3.8 mL, 29.0 mmol). The cold bath is removed, the reaction mixture is stirred for 1 hour, and then filtered. The filtrate is kept cold and used in the next step. To an ice-cold, stirred mixture of ether (110 mL) and potassium



hydroxide (40%, 35 mL) is slowly added 1-methyl-3-nitro-1-nitrosoguanidine (8.40 g, 57.0 mmol). The reaction mixture is stirred until gas evolution ends. The organic phase is separated and slowly added to an ice-cold, stirred mixture of the mixed anhydride filtrate from step 2. After the reaction mixture is stirred for 1 hour, nitrogen is bubbled into the mixture for 10 minutes. The resulting mixture is concentrated under reduced pressure, diluted with ethyl acetate (200 mL), and washed with water (100 mL). The organic phase is washed with saturated sodium bicarbonate and saline, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the diazoketone, which is carried on without purification or characterization. To an ice-cold, stirred mixture of diazoketone in ether (100 mL) is added hydrobromous acid (48%, 4 mL, 73 mmol). The cold bath is removed, the reaction mixture stirred for 30 minutes, and partitioned between ether and water. The organic phase separated and washed with saturated sodium bicarbonate and saline, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give tert-butyl (1S)-1-[4-(benzyloxy)benzyl]-3-bromo-2-oxopropylcarbamate (IV) which is used without further purification or characterization. To a -78 degrees C, stirred mixture of tert-butyl (1S)-1-[4-(benzyloxy)benzyl]-3-bromo-2-oxopropylcarbamate (IV) in a isopropanol/THF (2/1, 150 mL) is slowly added sodium borohydride (1.15 g, 30.0 mmol). The reaction mixture is stirred for 30 minutes followed by the addition of water (30 mL). The resulting mixture is warmed to 20-25 degrees C and concentrated under reduced pressure in a water bath not exceeding 30 degrees C. The crude residue is dissolved in ethyl acetate and washed with water and saline. The organic phase is dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the bromohydrin as a solid. To an ice-cold, stirred mixture of bromohydrin in ethanol (150 mL) and ethyl acetate (100 mL) is added a

potassium hydroxide (1 N) ethanol mixture (36 mL, 36 mmol). The cold bath is removed and the reaction mixture is stirred for 30 minutes. The resulting mixture is partitioned between ethyl acetate and water. The organic phase is separated and  
5 washed with saline, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica; hexanes/ethyl acetate, 5/1) gives tert-butyl  
(1S)-2-[4-(benzyloxy)phenyl]-1-[(2S)-oxiranyl]ethylcarbamate (V, as a 8/1 mixture of diastereomers),  
10 NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.44-7.32, 7.14, 6.93, 5.07, 4.45, 3.61, 3.00-2.60 and 1.39.

Step 2: A mixture of 4-benzyloxybutyric acid (2.69 g, 13.8 mmol), propylamine (0.82 g, 13.8 mmol), HOBt (2.05 g, 15.2 mmol), *N*-methylmorpholine (1.68 g, 16.6 mmol) and EDC (2.91 g,  
15 15.2 mmol) in DMF (6 mL) is stirred at 20-25 degrees C for 18 hours. The mixture is diluted with ethyl acetate (40 mL) and washed with water (10 mL), hydrochloric acid (1 N, 10 mL), saturated sodium bicarbonate (10 mL), and saline (10 mL). The organic phase is separated, dried over magnesium sulfate,  
20 filtered, and concentrated under reduced pressure to provide 4-(benzyloxy)-*N*-propylbutanamide (2.59 g), APCI-MS (*m/z*) [*M* + *H*]<sup>+</sup> = 236.

Step 3: To an ice-cold, stirred mixture of 4-(benzyloxy)-*N*-propylbutanamide (2.59 g, 11.0 mmol) in THF (8 mL) is added  
25 lithium aluminum hydride (0.54 g, 14.3 mmol). The reaction mixture is heated to 40-50 degrees C for 5 hours. The cooled reaction mixture is quenched with water (0.5 mL), sodium hydroxide (2 N, 1.0 mL), and saline (0.5 mL) then diluted with ether (30 mL). The precipitate that formed is filtered off,  
30 and the ether phase dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give *N*-[4-(benzyloxy)butyl]-*N*-propylamine (2.41 g), APCI-MS (*m/z*): 222 [*M* + *H*]<sup>+</sup>.

Step 4: A mixture of N-[4-(benzyloxy)butyl]-N-propylamine (2.31 g, 10.44 mmol), 3-(ethoxycarbonyl)-5-methylbenzoic acid (2.18 g, 10.44 mmol), HOBt (1.56 g, 11.49 mmol), N-methylmorpholine (1.37 mL, 12.52 mmol), and EDC (2.20 g, 11.49 mmol) in DMF (12 mL) is stirred at 20-25 degrees C for 18 hours. The reaction mixture is diluted with ethyl acetate (80 mL) and washed with water (2 x 20 mL), hydrochloric acid (1 N, 20 mL), saturated sodium bicarbonate (20 mL) and saline (20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica; hexanes/ethyl acetate, 1/1) gives ethyl 3-[[[4-(benzyloxy)butyl](propyl)amino]carbonyl]-5-methylbenzoate (1.79 g), NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  7.80, 7.64, 7.40, 7.38-7.16, 4.50-4.43, 4.34-4.29, 3.53-3.30, 3.20-3.06, 2.41-2.36, 1.70-1.40, 1.36-1.29, 0.94-0.84 and 0.82-0.72; APCI-MS ( $m/z$ )  $[M + H]^+ = 412$ .

Step 5: To a mixture of ethyl 3-[[[4-(benzyloxy)butyl](propyl)-amino]carbonyl]-5-methylbenzoate (1.75 g, 4.25 mmol) in THF/ethanol/water (1/2/1, 30 mL) is added lithium hydroxide (0.31 g, 12.76 mmol). The reaction mixture is stirred for 2 h and then acidified to pH = 3 with concentrated hydrochloric acid (0.5 mL). The reaction mixture is extracted with ethyl acetate (2 x 30 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 3-[[[4-(benzyloxy)butyl](propyl)-amino]carbonyl]-5-methylbenzoic acid (IX, 1.63 g), ESI-MS ( $m/z$ )  $[M + H]^+ = 384$ .

Step 6: A mixture of tert-butyl (1S)-2-[4-(benzyloxy)phenyl]-1-[(2S)-oxiranyl]ethylcarbamate (V, 1.58 g, 4.28 mmol) and 3-methoxybenzylamine (VI, 825 microliter, 6.42 mmol) in isopropanol (45 mL) is heated to 90 degrees C for 4 hours. Upon cooling to 20-25 degrees C, the reaction mixture is concentrated under reduced pressure. Purification by flash chromatography (silica; methylene chloride/methanol/ammonium

hydroxide 98/1/1 to 95/:4/1) gives tert-butyl (1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (VII, 1.97 g), NMR (300 MHz, MeOH- $d_4$ ):  $\delta$  7.41-6.79, 5.05, 4.33-3.33, 3.74, 3.54, 3.03-2.46 and 1.29; ESI-MS ( $m/z$ )  $[M + H]^+ = 507$ .

Step 7: tert-Butyl (1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (VII, step 6, 2.34 g, 4.62 mmol) in dioxane (10 mL) is treated with hydrochloric acid (12 mL of a 4.0 M mixture in dioxane, 48 mmol) for 2 hours. The precipitate that forms is collected by filtration, washed with ether, and dried under reduced pressure overnight to give (2R,3S)-3-amino-4-[4-(benzyloxy)phenyl]-1-[(3-methoxybenzyl)amino]-2-butanol hydrochloride (VIII), NMR (300 MHz, MeOH- $d_4$ ):  $\delta$  7.44-6.96, 5.05, 4.21, 3.83, 3.65) and 3.21-2.77; ESI-MS ( $m/z$ )  $[M + H]^+ = 407$ .

Step 8: To an ice-cold, stirred mixture of 3-[[[4-(benzyloxy)butyl](propyl)amino]carbonyl]-5-methylbenzoic acid (IX, 310 mg, 0.809 mmol), (2R,3S)-3-amino-4-[4-(benzyloxy)phenyl]-1-[(3-methoxybenzyl)amino]-2-butanol hydrochloride (VIII, 359 mg, 0.809 mmol), and bromotripyrrolidinophosphonium hexafluorophosphate (415 mg, 0.890 mmol) in methylene chloride (10 mL) is added diisopropylethylamine (285 microL, 1.62 mmol) dropwise. The resulting mixture is stirred at 0 degrees C for 30 minutes and then warmed to 20-25 degrees C. After 4 hours, the reaction is concentrated under reduced pressure and is partitioned between ethyl acetate and water. The aqueous phase is separated and extracted with ethyl acetate (3 x 15 mL), the combined organic phases are dried over magnesium sulfate, and concentrated under reduced pressure. The concentrate is purified by flash chromatography (silica; methylene chloride/methanol/ammonium hydroxide 96/3/0.5) to give  $N^1$ -{(1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}- $N^3$ -[4-(benzyloxy)butyl]-5-methyl- $N^3$ -propylisophthalamide (X)

NMR (300 MHz, Acetone- $d_6$ ):  $\delta$  7.99-6.74), 5.01 4.51-4.29, 4.36, 4.01, 3.80, 3.55-3.16, 2.98-2.82, 2.65-2.62, 2.36, 1.85-1.29, 1.01 and 0.68; ESI-MS ( $m/z$ )  $[M + H]^+ = 772$ .

Step 9. A mixture of  $N^1$ -{(1S,2R)-1-[4-(benzyloxy)benzyl]-  
5 2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)- $N^3$ -[4-(benzyloxy)butyl]-5-methyl- $N^3$ -propylisophthalamide (X, 100 mg, 0.130 mmol) and palladium on carbon (10%, 100 mg) in absolute glacial acetic acid (5 mL) is shaken under an atmosphere of hydrogen at 35 psi for 5 hours. The resulting mixture is  
10 filtered through diatomaceous earth and washed with methanol. The combined filtrates are concentrated under reduced pressure. The concentrate is purified by flash column chromatography (silica; gradient of dichloromethane/methanol/ammonium hydroxide 97/3/0.05 to 93/7/0.05) to give the title compound: NMR (300  
15 MHz,  $CD_3OD$ ):  $\delta$  7.55-6.64, 4.19, 3.99-3.72, 3.63-3.36, 3.21-3.09, 2.79-2.69, 2.39, 1.90-1.40, 1.29 and 1.02-0.6; ESI-MS ( $m/z$ )  $[M + H]^+ = 592$ .

EXAMPLE 756  $N^1$ -{(1S,2R)-2-hydroxy-1-(4-hydroxybenzyl)-3-[(3-  
20 methoxybenzyl)amino]propyl)-5-methyl- $N^3$ , $N^3$ -dipropylisophthalamide (X)

Step 1. To a stirred mixture of 3-[(dipropylamino)-  
carbonyl]-5-methylbenzoic acid (IX, 150 mg, 0.570 mmol),  
(2R,3S)-3-amino-4-[4-(benzyloxy)phenyl]-1-[(3-  
25 methoxybenzyl)amino]-2-butanol hydrochloride (VIII, 274 mg, 0.571 mmol), *N,N*-diisopropylethylamine (400 microliter, 2.28 mmol), and HOBt (116 mg, 0.857 mmol) in dichloromethane (10 mL) is added EDC (165 mg, 0.857 mmol). The resulting mixture is stirred at 20-25 degrees C for 16 hours. The reaction mixture  
30 is partitioned between dichloromethane and water. The aqueous phase is separated and extracted with dichloromethane (3 x 15 mL). The combined organic phases are washed with water, dried (magnesium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica;

dichloromethane/methanol/ammonium hydroxide, 97/3/0.05) gives  $N^1$ -{ (1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-methyl- $N^3,N^3$ -dipropylisophthalamide, ESI-MS ( $m/z$ )  $[M + H]^+ = 652$ .

5        Step 2. A mixture of  $N^1$ -{ (1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-methyl- $N^3,N^3$ -dipropylisophthalamide (140 mg, 0.215 mmol) and palladium on carbon (10%, 140 mg) in absolute glacial acetic acid (5 mL) is shaken under an atmosphere of hydrogen at 35 psi for 5 hours  
10 The resulting mixture is filtered through diatomaceous earth and washed with methanol. The combined filtrates are concentrated under reduced pressure. The concentrate is purified by flash column chromatography (silica; methylene chloride/methanol/ammonium hydroxide gradient from 97/3/0.05 to  
15 93/7/0.05) to give the title compound, IR (KBr) 2962, 2931, 1611, 1594 and 1263  $cm^{-1}$ ; ESI-MS ( $m/z$ )  $[M + H]^+ = 562$ .

EXAMPLE 757         $N^1$ -{ (1S,2R)-1-benzyl-3-[[3-(2,4-dimethylphenyl)propyl]amino]-2-hydroxypropyl}-5-methyl- $N^3,N^3$ -dipropylisophthalamide (X)  
20

Step 1: A stirred mixture of tert-butyl (1S)-1-[(2S)-oxiranyl]-2-phenylethylcarbamate (V, 247 mg, 0.939 mmol), sodium carbonate (299 mg, 2.82 mmol), and 3-(2,4-dimethylphenyl)propylamine (VI, 628 mg, 2.82 mmol) is heated at  
25 reflux overnight. The reaction mixture is cooled to 20-25 degrees C and concentrated under reduced pressure. Purification by flash column chromatography (silica; methylene chloride/methanol/ammonium hydroxide, 98/2/1) gives tert-butyl (1S,2R)-1-benzyl-3-[[3-(2,4-dimethylphenyl)propyl]amino]-2-  
30 hydroxypropylcarbamate (VII), NMR (300 MHz,  $CD_3OD$ ):  $\delta$  7.22-7.16, 3.81, 3.18, 2.77, 2.54, 2.15, 2.13, 1.89 and 1.23.

Step 2: To a stirred mixture of tert-butyl (1S,2R)-1-benzyl-3-[[3-(2,4-dimethylphenyl)propyl]amino]-2-hydroxypropylcarbamate (VII, 180 mg, 0.423 mmol) in dioxane (2

mL) is added hydrochloric acid (0.32 mL of a 4 N mixture in dioxane, 1.27 mmol). The reaction mixture is stirred overnight and concentrated under reduced pressure to give (2R,3S)-3-amino-1-([3-(2,4-dimethylphenyl)propyl]amino)-4-phenyl-2-butanol hydrochloride (VIII), NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.14, 3.73, 2.70, 2.32 and 1.86.

Step 3: To a stirred mixture of (2R,3S)-3-amino-1-([3-(2,4-dimethylphenyl)propyl]amino)-4-phenyl-2-butanol hydrochloride (VIII, 163 mg, 0.411 mmol), 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (IX, 108 mg, 0.411 mmol), HOBt (55 mg, 0.411 mmol), and *N*-methylmorpholine (133 mg, 1.32 mmol) in methylene chloride (5 mL) is added EDC (142 mg, 0.740 mmol). The reaction mixture is stirred overnight and then partitioned between ethyl acetate and water. The organic phase is washed with hydrochloric acid (1 N), saturated sodium bicarbonate, saline, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica; methylene chloride/methanol/ammonium hydroxide, 95/5/1) gives the title compound, IR (ATR): 3299, 2930 and 1614 cm<sup>-1</sup>; APCI-MS (*m/z*) [*M* + *H*]<sup>+</sup> = 572.

EXAMPLE 765 N<sup>3</sup>-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-4-methyl-N<sup>1</sup>,N<sup>1</sup>-dipropylisophthalamide (X)

3-Bromo-4-methylbenzoic acid (10.94 g, 43.25 mmol), copper(I)cyanide (7.75 g, 86.5 mmol) and 1-methyl-2-pyrrolidinone (75 mL) are heated to 160 degrees C overnight. The mixture is cooled and vacuum distilled to give a residue which is stirred in hydrochloric acid (6N, 60 mL) for 10 minutes. The resulting solid is collected by filtration, washed with water, ether, and dried. The solid is heated to 90 degrees C in sodium hydroxide (2N, 250 mL) for 3 hours and the mixture is then cooled and stirred overnight at 20-25 degrees

C. The reaction is acidified to about pH 3 with concentrated hydrochloric acid which gives a precipitate. The solids are collected by filtration and washed with water, then triturated in boiling water, filtered and dried in a vacuum oven at 60  
5 degrees C. The solid is dissolved in methanol (75 ml) and concentrated hydrochloric acid (5 ml) is added and the mixture is refluxed overnight. The mixture then is cooled and concentrated under reduced pressure. Chromatography (silica gel; methanol/methylene chloride, 8/92) gives 5-  
10 (methoxycarbonyl)-2-methylbenzoic acid.

To 5-(methoxycarbonyl)-2-methylbenzoic acid (250 mg, 1.3 mmol) and triethylamine (0.72 ml, 5.2 mmol) in methylene chloride (14 ml) is added diethylcyanopyrocarbonate (90%, 0.24 ml, 1.4 mmol) with stirring. After 1 minute, (2R,3S)-3-amino-  
15 1-[(3-methoxybenzyl)amino]-4-phenyl-2-butanol dihydrochloride (VIII, 485 mg, 1.3 mmol) is added and the reaction is stirred overnight. The mixture is concentrated followed by chromatography (silica gel; methanol/methylene chloride 8/92) to afford  
20 3-[[[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino]carbonyl]-4-methylbenzoate.

3-[[[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino] carbonyl]-4-methylbenzoate (200 mg, 0.42 mmol) is treated with lithium hydroxide (39 mg, 0.96 mmol) in tetrahydrofuran/methanol/water (2/1/1, 2 ml), and  
25 the mixture stirred overnight at 20-25 degrees C. The mixture is decanted and the supernatant concentrated to give 3-[[[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino]carbonyl]-4-methylbenzoic acid.

3-[[[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino] carbonyl]-4-methylbenzoic  
30 acid (124 mg, 0.27 mmol) is dissolved in triethylamine (0.07 ml, 0.54 mmol) and methylene chloride (3 ml) and treated with diethylcyanopyrocarbonate (90%, 0.06 ml, 0.32 mmol) with stirring for 2 minutes. Dipropylamine (0.04 ml, 0.32 mmol) is



added and stirring continued overnight. The organic phase is diluted with methylene chloride and washed with saturated sodium bicarbonate (2 X 50 ml) and saline (50 ml) then dried over anhydrous sodium sulfate, filtered and concentrated.  
5 Chromatography (silica gel; methanol/methylene chloride, 8/92) gives the title compound, MS  $[M+H]^+ = 546.3$ .

EXAMPLE 766 N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-(2-furyl)-5-methylbenzamide (X)  
10 N-((1R,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-bromo-5-methylbenzamide (X, EXAMLE 761, 295 mg, 0.59 mmol), 2-furanylboronic acid (133 mg, 1.19 mmol) and sodium carbonate (366 mg, 2.95 mmol) are  
15 combined in dimethylformamide (5 ml) and sparged under a flow of nitrogen for 15 minutes. Tetrakis(triphenylphosphino) palladium (136 mg, 0.12 mmol) is added and the mixture heated to 100 degrees C overnight. The mixture is cooled to 20-25 degrees C, diluted with chloroform (50 ml) and extracted with  
20 water (3 x 100 ml). The organic phase is separated and washed with saturated sodium bicarbonate (2 x 100 ml) and saline (100 ml), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressue. The residue is chroumatographed (silica gel; methanol/methylene chloride,  
25 8/92) to give the title compound, MS  $[M+H]^+ = 485.3$ .

EXAMPLE 792 2-Butylcyclopropylamine hydrochloride (VI)  
A solution of triethylphosphonoacetate (22.4 g, 0.1 mol) in 13 mL of diglyme is added to a mixture of 13 mL of  
30 diglyme and sodium hydride (60%, 5.7 g, 0.12 mol) in mineral oil. When hydrogen evolution ceased, 1,2-epoxyhexane (12 g, 0.12 mol) in diglyme (12 mL) is added. The mixture is stirred for 1 day at 25 degrees C and 3 hours at 140 degrees C. A mixture of sodium hydroxide (15 g in 25 mL of water)

is added in the cold. The mixture is refluxed 15 hours, diluted with cold water (100 mL), and washed with ether (3 x 50 mL). Acidification to pH = 2 with sulfuric acid (25%), extraction with ether (5 x 25 mL), drying the ether over  
5 anhydrous sodium sulfate, filtration and concentration gives 2-butylcyclopropanecarboxylic acid. The acid (5.0 g, 0.035 mmol) in dichloromethane (15 mL) is heated with thionyl chloride (5.1 g, 3.1 mL) for 15 hours at 60 degrees C. The reaction mixture is distilled (76 degrees C- 80 degrees C)  
10 to give the acid chloride which is dissolved in acetone (15 mL), cooled to -10 degrees C and treated with sodium azide (2.2 g, 33.8 mmol) in water (5 mL). The reaction mixture is stirred at -10 degrees C for another 1 hour and then poured onto ice/water, extracted with ether (3x10 mL), dried, and  
15 cautiously evaporated to dryness at 20-25 degrees C under reduced pressure. The residue is dissolved in toluene (15 mL) and carefully warmed to 100 degrees C while vigorously stirring for 1 hour. Concentrated hydrochloric acid (7 mL) is added and the reaction mixture is refluxed for 15  
20 minutes. The acidic layer is evaporated to dryness to give the title compound,  $MH^+ = 114.2$ .

EXAMPLE 793      2-Aminomethyl-3-methylfuran (VI)

3-Methylfuroic acid (4.0 g, 32 mmol) is dissolved in  
25 DMF (10 mL) at 20-25 degrees C, and 1,1-carbonyldiimidazole (5.7 g, 35 mmol) is added. After 15 minutes, ammonia is bubbled into the mixture for approximately 2 minutes. This mixture is stirred at 20-25 degrees C for 2 hours then the mixture is concentrated under reduced pressure. The residue  
30 is partitioned between ethyl acetate and 10% aqueous citric acid. The layers are separated, and the aqueous layer extracted with additional ethyl acetate (2 x). The combined organic phases are washed with saturated sodium bicarbonate, then saline and dried over magnesium sulfate, filtered and

concentrated. Crystals formed upon standing, which are isolated by filtration and washing with a small amount of ethyl acetate/hexanes (80/20), MS(ESI): MH+: 126.1. 3-Methylfuroic amide (317 mg, 2.5 mmol) is dissolved in dry THF (5 mL). Lithium aluminum hydride (230 mg, 6.0 mmol) is added in one portion, and the mixture heated to reflux overnight. The mixture is cooled to 0 degrees C, and quenched by addition of THF/water (50/50). The mixture is then diluted with THF, and filtered through diatomaceous earth. The filtrate is concentrated to give the title compound, MS(ESI): (M-H)+: 109.1.

EXAMPLE 7944-Aminomethyl-3,5-dimethylisoxazole (VI)

4-Chloromethyl-3,5-dimethylisoxazole (700 mg, 4.8 mmol) is suspended in concentrated aqueous ammonia at 20-25 degrees C, and vigorously stirred overnight. The reaction mixture is extracted with isopropyl alcohol/chloroform (10/90, 2 x). The combined organic phases are concentrated under nitrogen flow. The residue is purified by flash chromatography methanol/methylene chloride (5-20%, 1% triethylamine) to give the title compound, MR (CDCl<sub>3</sub>, 300 MHz) delta 3.62, 2.37, 2.29, and 1.44.

EXAMPLE 795 5-Hydroxymethyl-2-(2-methylpropyl) thiazole (VI)

Isovalerothioamide is synthesized according to the procedure in *J. Med. Chem.* 41, 602-617 (1998). Isovaleramide (10 g, 9.9 mmol) is suspended in dry ether (400 mL), then phosphorous(V) sulfide (4.4 g, 0.99 mmol) is added in portions. This is vigorously stirred at 20-25 degrees C for 2 hours, then filtered. The filtrate is concentrated under reduced pressure and the residue used without further purification: MS(ESI): MH+: 118.1.

Isovalerothioamide (6.0 g, 51 mmol) and ethyl formylchloroacetate (*Heterocycles* 32 (4), 693-701, (1991), 5.0 g, 33 mmol) are dissolved in dry DMF (20 mL), and heated to 95 degrees C for 4 hours. The reaction is subsequently cooled to 0 degrees C, and cold water (50 mL) is added. The mixture is basified to pH = 8 with solid sodium bicarbonate, then extracted with ether (3 x 35 mL). The combined organic extracts are washed with water, then saline and dried over magnesium sulfate, filtered, and concentrated. The residue is purified by flash chromatography (ethyl acetate/hexanes 4-10% elution) to give the desired product. NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  8.27, 4.45-4.30, 3.70-3.50, 3.00-2.80, 2.30-2.10, 1.40-1.20, and 1.10-0.90.

A solution of ethyl 2-(2-methylpropyl)thiazole-5-carboxylate (2.05 g, 9.6 mmol) in THF (10 mL) is added dropwise with stirring to a suspension of lithium aluminum hydride (730 mg, 19 mmol) in dry THF (50 mL) at 0 degrees C. Upon complete addition, the reaction mixture is allowed to stir at 20-25 degrees C. The reaction mixture is cooled to 0 degrees C, and water (0.75 mL), aqueous sodium hydroxide (15%, 0.75 mL), and water (2.25 mL) is added in succession. This mixture is stirred at 0 degrees C for 1 hour, then filtered through diatomaceous earth, (THF and chloroform). The filtrate is concentrated to give 5-hydroxymethyl-2-(2-methylpropyl)thiazole, MS(ESI): MH<sup>+</sup>: 172.1.

EXAMPLE 796 3-(2-Methylpropyl)-5-aminomethylisoxazole (VI)

Isovaleraldehyde (5.4 mL, 50 mmol) and hydroxylamine hydrochloride (3.5 g, 50.4 mmol) are vigorously stirred in water (6 mL). To this is added a solution of sodium carbonate (2.65 g, 25 mmol) in water (15 mL). This is vigorously stirred overnight. The mixture is extracted with ether. The organic layer is washed with water, then dried over sodium sulfate,

filtered and concentrated. This is used in subsequent reactions without further purification: MS(ESI): MH+: 102.1.

Propargylamine (8.0 mL, 117 mmol) is dissolved in methylene chloride (60 mL), and di-*tert*-butyl dicarbonate (25 g, 114 mmol) is added. This is stirred overnight, and concentrated to provide the BOC-protected propargylamine, which is used without further purification: MS(ESI): MNa+: 178.0.

BOC-propargylamine (6.2 g, 39.7 mmol) and isovaleroxime (3.97 g, 39.3 mmol) is dissolved in methylene chloride (60 mL), and triethylamine (0.55 mL, 3.95 mmol) is added. This is cooled to 0 degrees C, and bleach (5% aqueous solution, 59.1 g) is added dropwise with vigorous stirring. After addition is complete, the mixture is allowed to warm to 20-25 degrees C over 22 hours. The layers are separated, and the aqueous layer is extracted with methylene chloride (2 x). The combined organic extracts are washed with saline, dried over magnesium sulfate, filtered and concentrated. The residue is purified by chromatography (silica gel, ethyl acetate/hexanes 5-10%) to give the BOC-protected title compound, MS(ESI): MH+: 255.3.

BOC-protected 3-(2-methylpropyl)-5-aminomethylisoxazole (2.4 g, 9.3 mmol) is dissolved in methylene chloride (10 mL) and treated with trifluoroacetic acid (10 mL) at 20-25 degrees C. This is stirred at 20-25 degrees C for 70 minutes, then concentrated. The product is dissolved in methylene chloride, and washed with aqueous potassium carbonate (1 M) until basic (pH = 11). The organic layer is isolated, dried over sodium sulfate, filtered and concentrated to give the title compound: MS(ESI): MH+: 155.2.

EXAMPLE 797 *tert*-butyl (3R)-2-oxo-1-propylazepanylcarbamate (VI)

To N-*t*-Boc-D-Lys-OH (10 g, 41.4mmole) in DMF (4 liters) is added benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (BOP, 18.3 g, 41.4mmole) and sodium

bicarbonate (17.4 g, 206.8mmole); the reaction is stirred at 20-25 degrees C for 12 hours. The reaction is then concentrated to 50 ml volume and diluted with ethyl acetate and washed with sodium bicarbonate 3x, water, 1M potassium bisulfate and brine, dried and concentrated. Purification by chromatography on silica gel afforded 5.05 g of the tert-butyl (3R)-2-oxoazepanylcarbamate as a solid; the procedure employed is similar to that described in *J.Med.Chem.* 1999, 4193. M+H-(t-Boc) (m/e=129.2), M+Na (m/e=251.1).

To the above lactam (2 g, 8.77mmole) in dry THF (20 ml) is added n-butyllithium /hexane (2.5 M, 5.3 ml, 13.2 mmole) at -78 degrees C, the reaction is stirred for 1 hour and 1-bromopropane (3.2 ml, 35.1 mmole) is added. The reaction is stirred for 1 hour and the cold bath removed and stirring continued for another 16 hours. Tetrabutylammonium iodide (0.49 g, 2.63mmole) is added and the reaction stirred for another 16 hours. The reaction is partitioned between ethyl acetate/hydrochloric acid + ice + water, the mixture is washed with water and saline and concentrated. Purification by chromatography on silica gel afforded the title compound, MS (M+Na+) 293.3.

EXAMPLE 798  $N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-5-methyl- $N^3,N^3$ -dipropylisophthalamide (X)

Following the procedure described in *J. Am. Chem. Soc.* 1986, 3150, the trifluoroacetic acid salt of  $N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-5-methyl- $N^3,N^3$ -dipropylisophthalamide (92.9 mg, 0.117 mmol) is dissolved in triethylamine (0.2 M, 0.6 mL) before the addition of  $PdCl_2(PPh_3)_2$  (3.3 mg, 0.005 mmol), and copper (I) iodide (1.1 mg, 0.006 mmol). The reaction is heated to reflux. While the reaction is refluxing, trimethylsilylacetylene (0.02 ml, 0.14

mmol) is added via syringe. The reaction is refluxed for 3 hour under N<sub>2</sub> (g), and the reaction cooled to 20-25 degrees C before partitioning between aqueous sodium bicarbonate and ethyl acetate. The product is extracted with ethyl acetate (3 x),  
5 washed with saline, dried over sodium sulfate, and filtered before the removal of solvent under reduced pressure.

The TMS protected acetylene (0.117 mmol) is dissolved in methanol (0.2 M, 0.5 mL) before the addition of potassium hydroxide (1M, 0.7 mL, 0.7 mmol). The reaction is stirred at  
10 20-25 degrees C for 6 hours, at which point the mixture is partitioned between sodium bicarbonate and ethyl acetate. The product is extracted with ethyl acetate (3 x), washed with saline, dried over sodium sulfate, and filtered before the removal of solvent under reduced pressure. Column  
15 chromatography (silica gel; 1.5-2 % isopropanol/chloroform under basic conditions; a few drops of ammonium hydroxide per 100 mL of elution solvent) gives the title compound, MS m/z (M+H)<sup>+</sup> = 576.3.

20 EXAMPLE 799 1-phenylcyclopropylamine (VI)

Following the procedure described in N.W. Werner et.al.,  
J. Org. Syn. Coll. Vol. 5, 273-276, sodium azide (0.915g, 14.1  
mmol) is slowly added to a solution of 1-phenyl-  
cyclopropanecarboxylic acid (1.0 g, 6.1 mmol) in concentrated  
5 sulfuric acid (5 ml) and dichloromethane (10 ml). The sodium  
sulfate precipitated out of solution. The reaction mixture is  
heated to 50 degrees C for 17 hours and then cooled to 0  
degrees C. The mixture is basified to pH = 11 with sodium  
hydroxide (1N) and extracted with dichloromethane (2 x). The  
10 organic layers are combined, dried over sodium sulfate,  
filtered and concentrated. The residue is purified by  
chromatography (silica gel; isopropyl alcohol/chloroform/  
ammonium hydroxide 4/95/1) to give the title compound, MS  
(ESI+) for  $C_9H_{11}N$   $m/z$  (M+H)<sup>+</sup> = 134.

15

EXAMPLE 800 7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine  
(VI)

7-Methoxy-1-tetralone (2.0 g, 11.3 mmol), hydroxylamine  
hydrochloride (1.56 g, 22.6 mmol) and sodium acetate (1.8g,  
20 22.6 mmol) are suspended in ethanol/water (3/1, 40 mL). The  
mixture is heated for 45 min. at 100 degrees C. The mixture is  
allowed to cool overnight and the precipitate obtained is  
filtered and washed with water to yield an intermediate oxime,  
MS (ES) (M+H): 192.1. The oxime is dissolved in glacial acetic  
25 acid (25 ml) and palladium/carbon (500 mg) is added and the  
mixture hydrogenated under 50 psi at 20-25 degrees C overnight.  
The catalyst is filtered over diatomaceous earth and washed  
with methanol. The combined filtrates are concentrated. The  
concentrate is triturated with ether to give the title  
30 compound, MS (CI) (M+H)<sup>+</sup>: 178.2.

Examples 1208-1214 and 1226

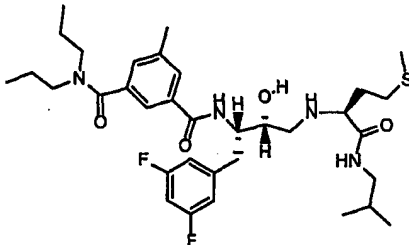
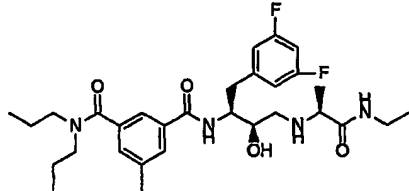
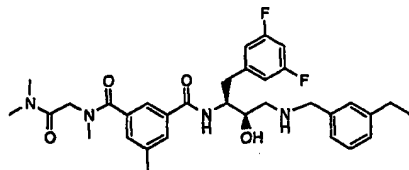


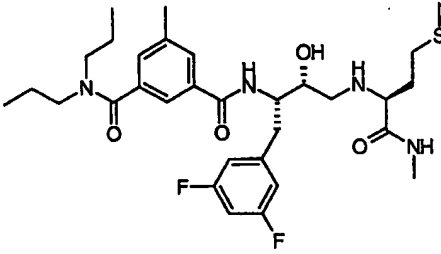
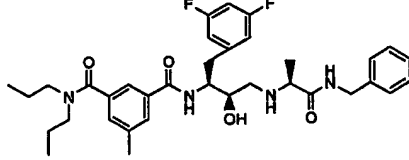
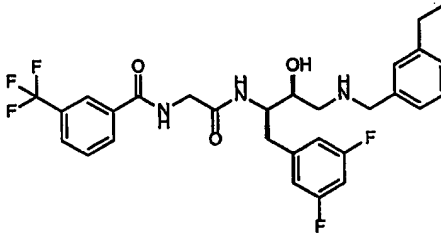
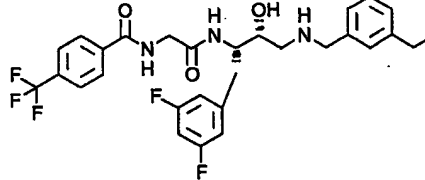
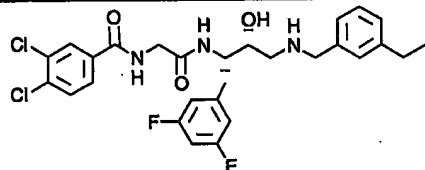
- 1,208       $N^1$ -(tert-butyl)- $N^3$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisophthalamide
- 5      1,209      5-bromo- $N^1$ -(tert-butyl)- $N^3$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isophthalamide
- 1,210      3-tert-butoxy-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide
- 1,211      3-tert-butoxy-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylbenzamide
- 10      1,212      N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[[trifluoromethyl)sulfonyl]amino}benzamide
- 1,213      N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(trifluoromethoxy)benzamide
- 15      1,214      N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-(trifluoromethoxy)benzamide
- 20      1,226       $N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(4-methyl-1,3-oxazol-2-yl)- $N^3$ , $N^3$ -dipropylisophthalamide       $(M+H)^+ = 647.5$

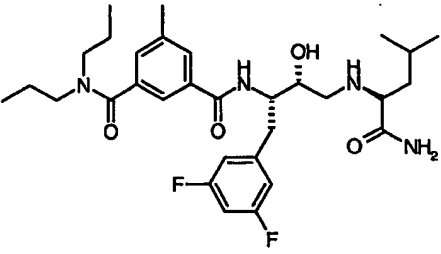
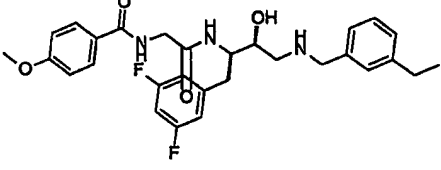
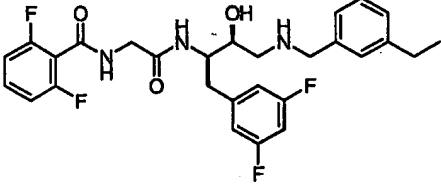
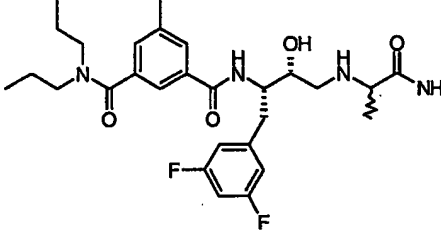
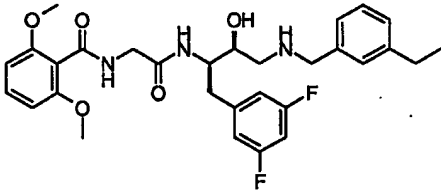
The compounds in the table immediately below were prepared essentially using the methods described above and illustrated below in the schemes.

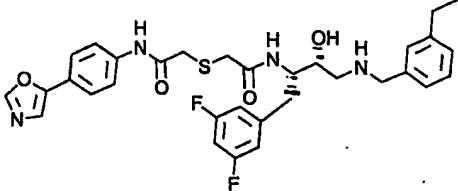
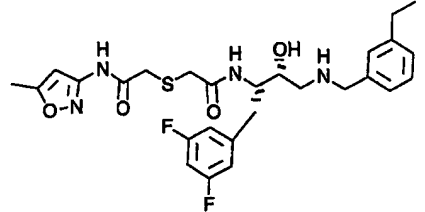
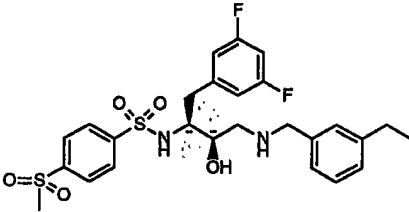
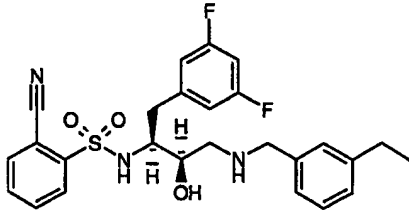
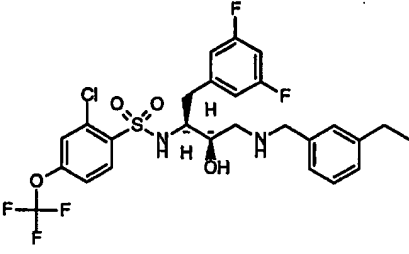
Compounds in this application were named using Chemdraw  
 5 Ultra version 6.0.2, which is available through  
 Cambridgesoft.co, 100 Cambridge Park Drive, Cambridge, MA  
 02140, Namepro version 5.09, which is available from ACD labs,  
 90 Adelaide Street West, Toronto, Ontario, M5H, 3V9, Canada,  
 or were derived from names generated using those programs.

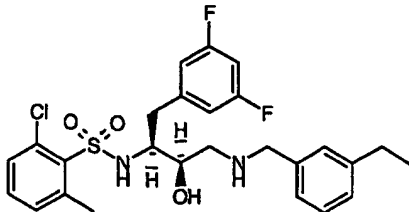
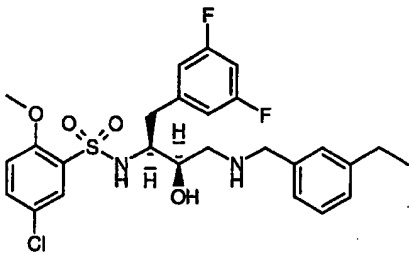
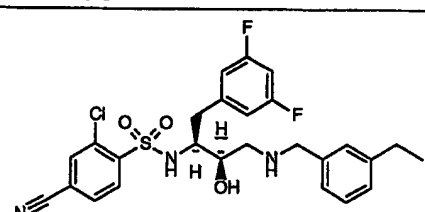
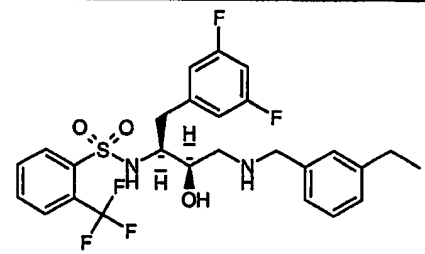
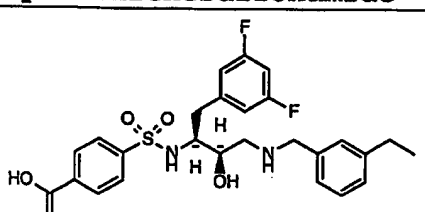
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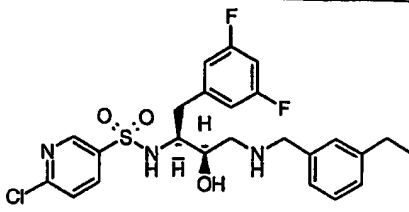
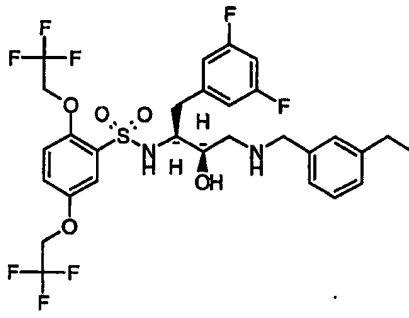
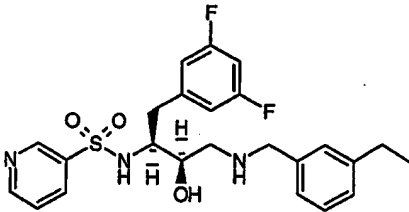
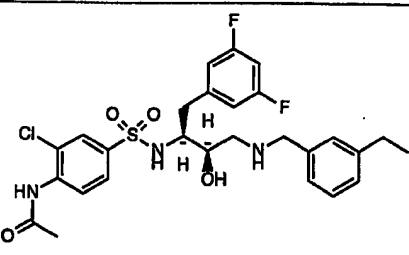
1260	 <p>N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1-isobutylcarbamoyl-3-methylsulfanyl-propylamino)-propyl]-5-methyl-N',N'-dipropyl-isophthalamide</p>
1261	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(1-ethylcarbamoyl-ethylamino)-2-hydroxy-propyl]-5-methyl-N',N'-dipropyl-isophthalamide</p>
1262	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-N'-dimethylcarbamoylmethyl-5,N'-dimethyl-isophthalamide</p>

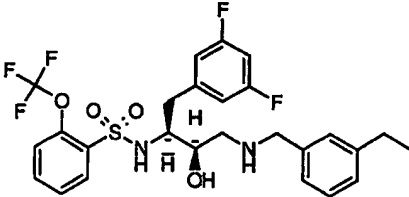
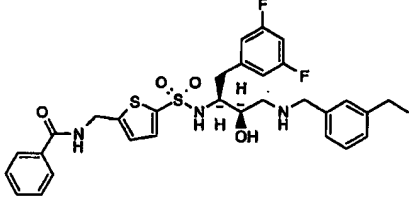
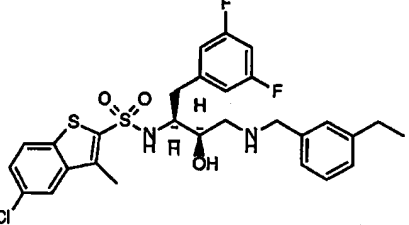
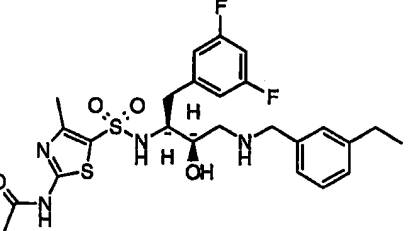
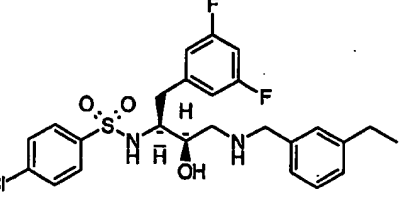
1263	 <p>N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1-methylcarbamoyl-3-methylsulfanyl-propylamino)-propyl]-5-methyl-N',N'-dipropyl-isophthalamide</p>
1264	 <p>N-[3-(1-Benzylcarbamoyl-ethylamino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-5-methyl-N',N'-dipropyl-isophthalamide</p>
1265	 <p>N-{[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylcarbamoyl]-methyl}-3-trifluoromethyl-benzamide</p>
1266	 <p>N-{[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylcarbamoyl]-methyl}-4-trifluoromethyl-benzamide</p>
1267	 <p>3,4-Dichloro-N-{[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylcarbamoyl]-methyl}-benzamide</p>

1268	 <p>N-[3-(1-Carbamoyl-3-methyl-butylamino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-5-methyl-N',N'-dipropyl-isophthalamide</p>
1269	 <p>N-{[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylcarbamoyl]-methyl}-4-methoxy-benzamide</p>
1270	 <p>N-{[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylcarbamoyl]-methyl}-2,6-difluoro-benzamide</p>
1271	 <p>N-[3-(1-Carbamoyl-ethylamino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-5-methyl-N',N'-dipropyl-isophthalamide</p>
1272	 <p>N-{[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylcarbamoyl]-methyl}-2,6-dimethoxy-benzamide</p>

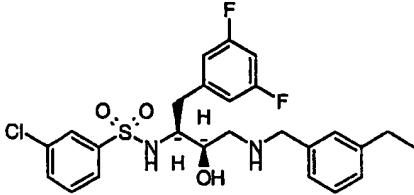
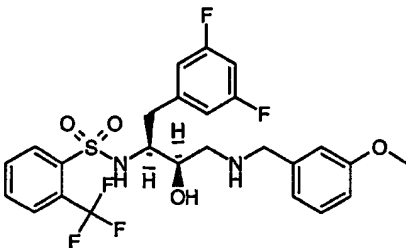
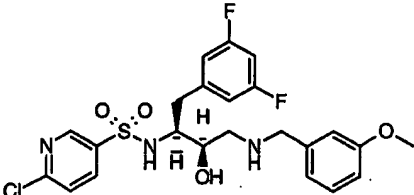
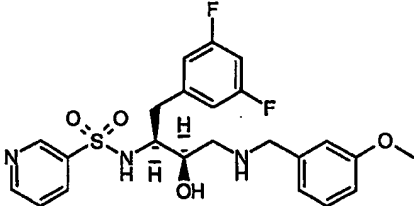
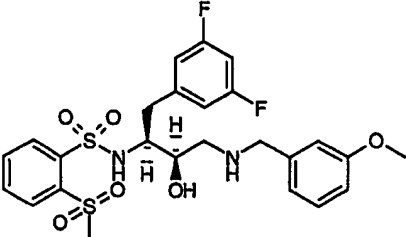
1273	 <p>2-([1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylcarbamoyl]-methylsulfanyl)-N-(4-oxazol-5-yl-phenyl)-acetamide</p>
1274	 <p>2-([1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylcarbamoyl]-methylsulfanyl)-N-(5-methyl-isoxazol-3-yl)-acetamide</p>
1275	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-4-methanesulfonyl-benzenesulfonamide</p>
1276	 <p>2-Cyano-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-benzenesulfonamide</p>
1277	 <p>2-Chloro-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-4-(trifluoromethoxy)benzenesulfonamide</p>

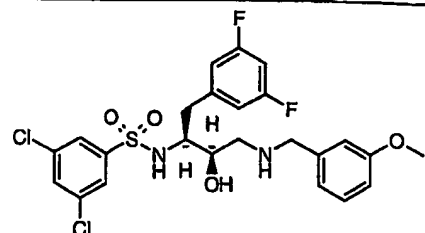
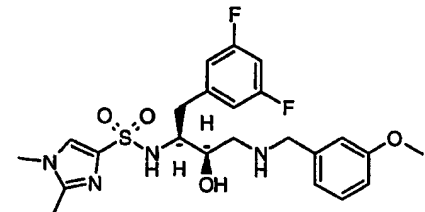
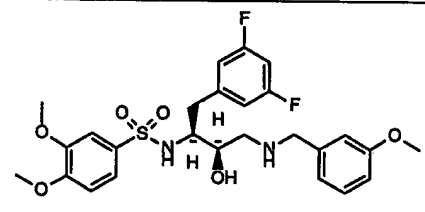
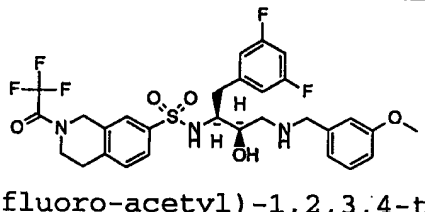
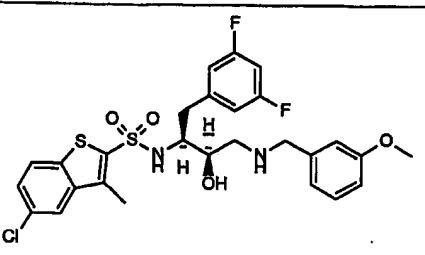
	trifluoromethoxy-benzenesulfonamide
1278	 <p>2-Chloro-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-6-methyl-benzenesulfonamide</p>
1279	 <p>5-Chloro-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-methoxy-benzenesulfonamide</p>
1280	 <p>2-Chloro-4-cyano-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-benzenesulfonamide</p>
1281	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-trifluoromethyl-benzenesulfonamide</p>
1282	 <p>4-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-benzenesulfonamide</p>

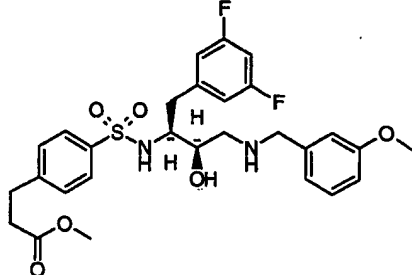
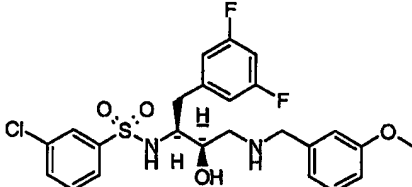
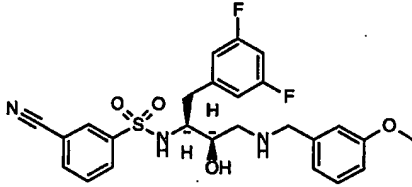
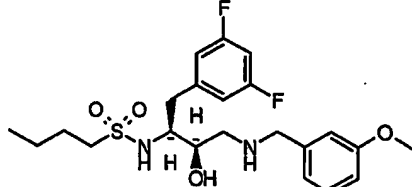
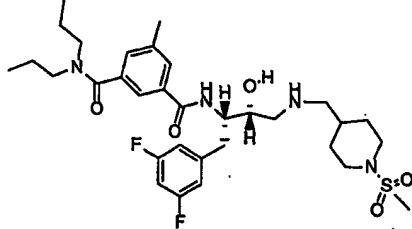
	benzylamino)-2-hydroxy-propylsulfamoyl]-benzoic acid
1283	 <p>6-Chloro-pyridine-3-sulfonic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1284	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2,5-bis-(2,2,2-trifluoro-ethoxy)-benzenesulfonamide</p>
1285	 <p>Pyridine-3-sulfonic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1286	 <p>N-{2-Chloro-4-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylsulfamoyl]-phenyl}-acetamide</p>

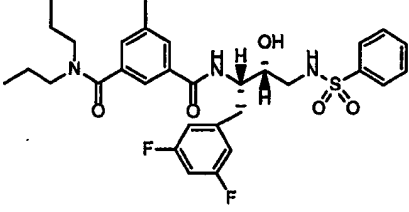
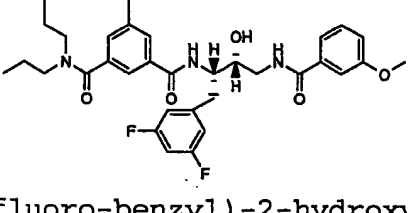
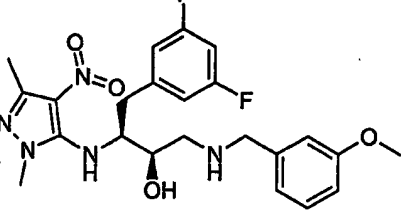
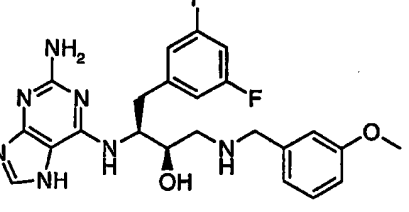
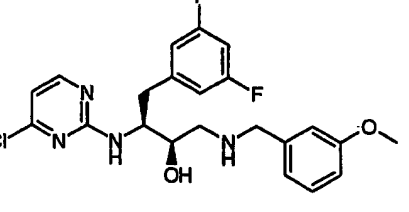
1287	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-trifluoromethoxy-benzenesulfonamide</p>
1288	 <p>N-{5-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylsulfamoyl]-thiophen-2-ylmethyl}-benzamide</p>
1289	 <p>5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1290	 <p>N-{5-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylsulfamoyl]-4-methyl-thiazol-2-yl}-acetamide</p>
1291	 <p>4-Chloro-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-benzenesulfonamide</p>

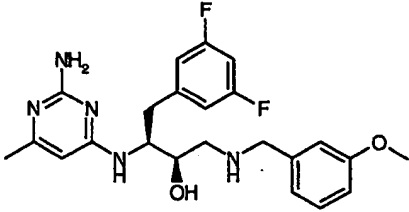
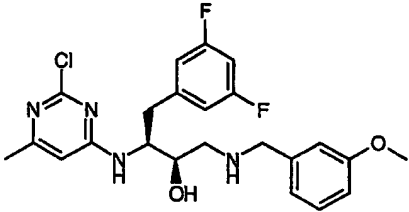
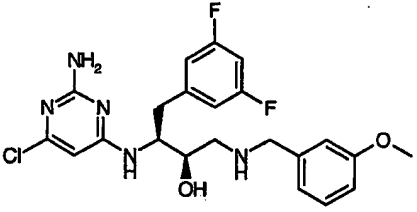
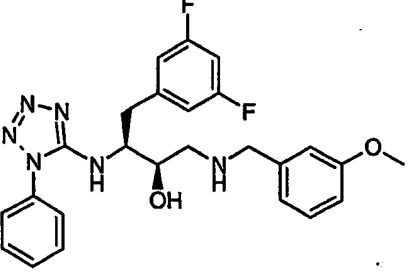
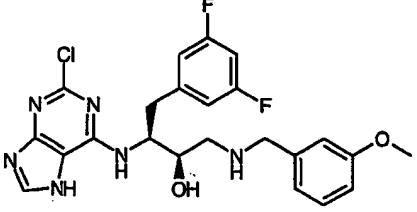


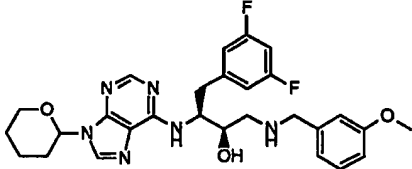
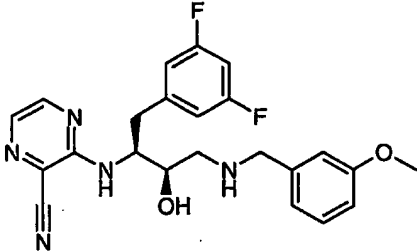
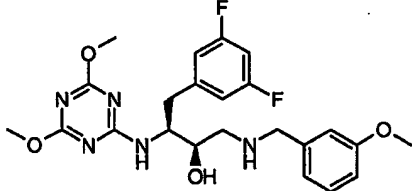
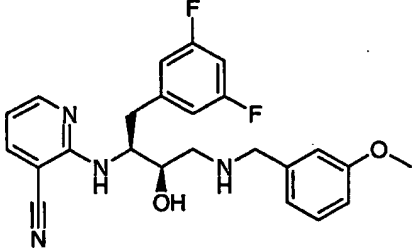
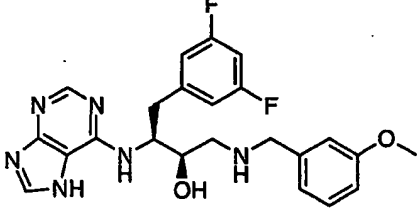
1292	 <p>3-Chloro-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-benzenesulfonamide</p>
1293	 <p>N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-2-trifluoromethyl-benzenesulfonamide</p>
1294	 <p>6-Chloro-pyridine-3-sulfonic acid [1-(3,5-difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-amide</p>
1295	 <p>Pyridine-3-sulfonic acid [1-(3,5-difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-amide</p>
1296	 <p>N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-2-methanesulfonyl-benzenesulfonamide</p>

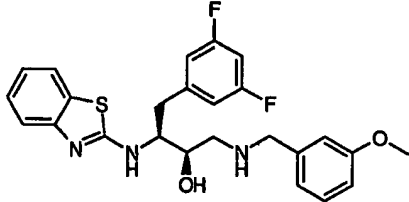
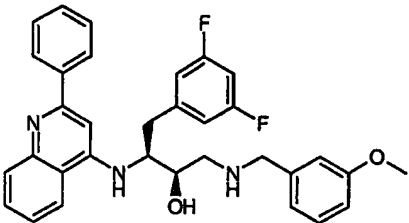
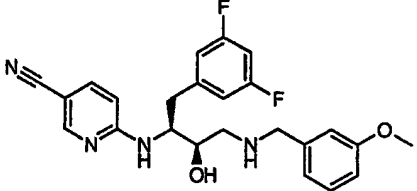
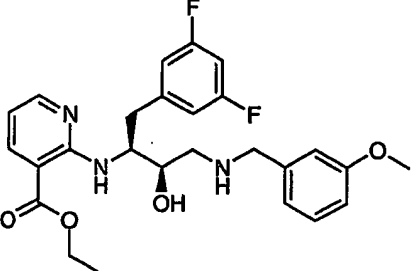
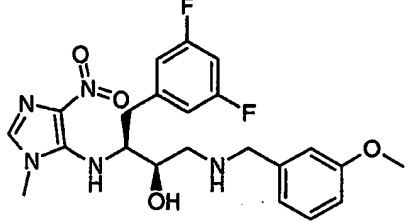
1297	 <p>3,5-Dichloro-N-[1-(3,5-difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-benzenesulfonamide</p>
1298	 <p>1,2-Dimethyl-1H-imidazole-4-sulfonic acid [1-(3,5-difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-amide</p>
1299	 <p>N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-3,4-dimethoxybenzenesulfonamide</p>
1300	 <p>2-(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydroisoquinoline-7-sulfonic acid [1-(3,5-difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-amide</p>
1301	 <p>5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [1-(3,5-difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-amide</p>

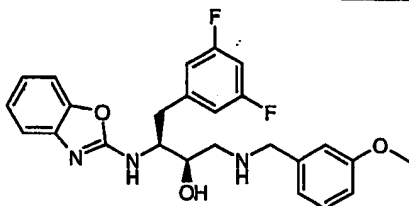
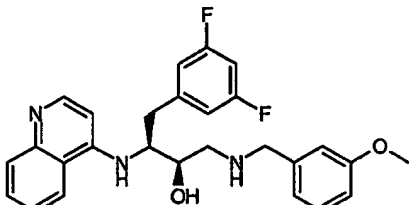
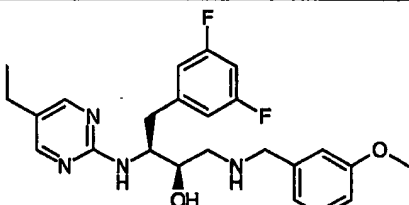
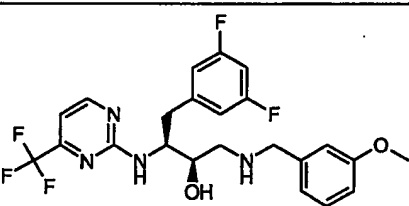
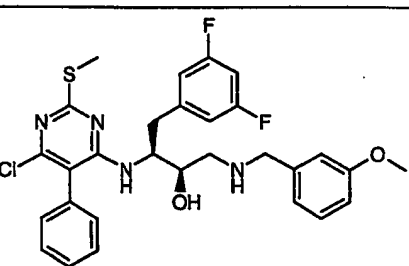
1302	 <p>3-{4-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propylsulfamoyl]-phenyl}-propionic acid methyl ester</p>
1303	 <p>3-Chloro-N-[1-(3,5-difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-benzenesulfonamide</p>
1304	 <p>3-Cyano-N-[1-(3,5-difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-benzenesulfonamide</p>
1305	 <p>Butane-1-sulfonic acid [1-(3,5-difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-amide</p>
1306	 <p>N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[(1-methanesulfonyl-piperidin-4-ylmethyl)-amino]-propyl}-5-methyl-N',N'-dipropyl-isophthalamide</p>

1307	 <p>N-[3-Benzenesulfonylamino-1-(3,5-difluorobenzyl)-2-hydroxy-propyl]-5-methyl-N',N'-dipropyl-isophthalamide</p>
1308	 <p>N-[1-(3,5-Difluorobenzyl)-2-hydroxy-3-(3-methoxy-benzoylamino)-propyl]-5-methyl-N',N'-dipropyl-isophthalamide</p>
1309	 <p>4-(3,5-Difluorophenyl)-3-(2,5-dimethyl-4-nitro-2H-pyrazol-3-ylamino)-1-(3-methoxy-benzylamino)-butan-2-ol</p>
1310	 <p>3-(2-Amino-7H-purin-6-ylamino)-4-(3,5-difluorophenyl)-1-(3-methoxy-benzylamino)-butan-2-ol</p>
1311	 <p>3-(4-Chloro-pyrimidin-2-ylamino)-4-(3,5-difluorophenyl)-1-(3-methoxy-benzylamino)-butan-2-ol</p>

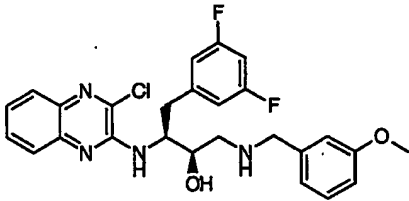
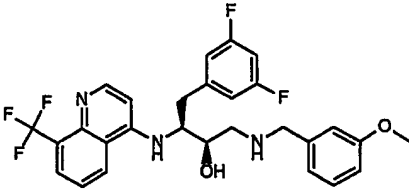
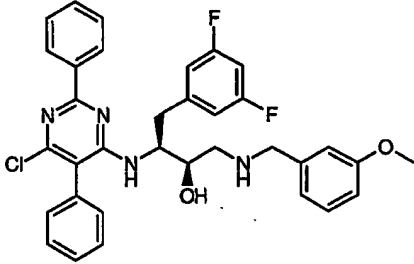
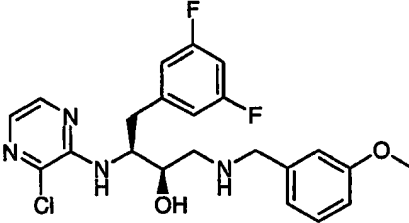
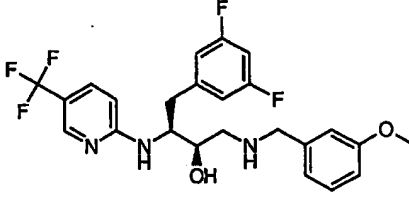
1312	 <p>3-(2-Amino-6-methyl-pyrimidin-4-ylamino)-4-(3,5-difluoro-phenyl)-1-(3-methoxy-benzylamino)-butan-2-ol</p>
1313	 <p>3-(2-Chloro-6-methyl-pyrimidin-4-ylamino)-4-(3,5-difluoro-phenyl)-1-(3-methoxy-benzylamino)-butan-2-ol</p>
1314	 <p>3-(2-Amino-6-chloro-pyrimidin-4-ylamino)-4-(3,5-difluoro-phenyl)-1-(3-methoxy-benzylamino)-butan-2-ol</p>
1315	 <p>4-(3,5-Difluoro-phenyl)-1-(3-methoxy-benzylamino)-3-(1-phenyl-1H-tetrazol-5-ylamino)-butan-2-ol</p>
1316	 <p>3-(2-Chloro-7H-purin-6-ylamino)-4-(3,5-difluoro-phenyl)-1-(3-methoxy-benzylamino)-butan-2-ol</p>

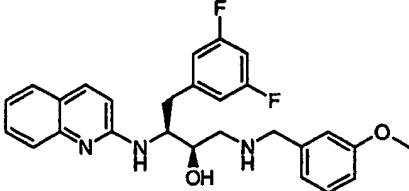
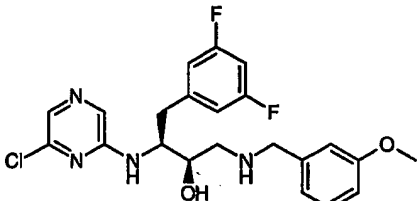
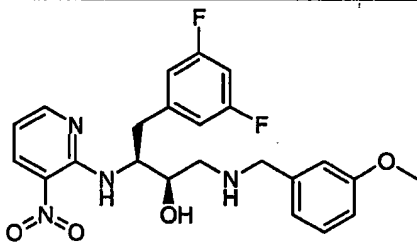
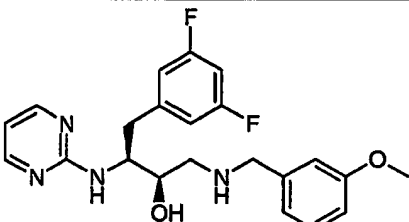
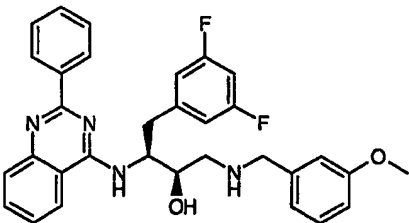
1317	 <p>4-(3,5-Difluoro-phenyl)-1-(3-methoxy-benzylamino)-3-[9-(tetrahydro-pyran-2-yl)-9H-purin-6-ylamino]-butan-2-ol</p>
1318	 <p>3-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propylamino]-pyrazine-2-carbonitrile</p>
1319	 <p>4-(3,5-Difluoro-phenyl)-3-(4,6-dimethoxy-[1,3,5]triazin-2-ylamino)-1-(3-methoxy-benzylamino)-butan-2-ol</p>
1320	 <p>2-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(3-methoxy-benzylamino)-propylamino]-nicotinonitrile</p>
1321	 <p>4-(3,5-Difluoro-phenyl)-1-(3-methoxy-benzylamino)-3-(7H-purin-6-ylamino)-butan-2-ol</p>

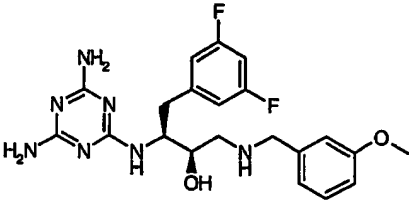
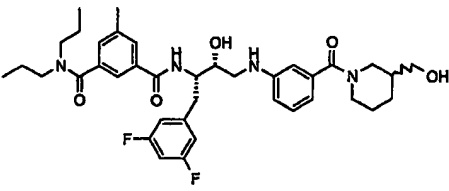
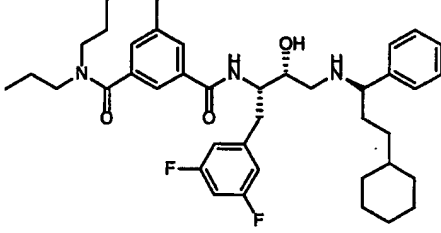
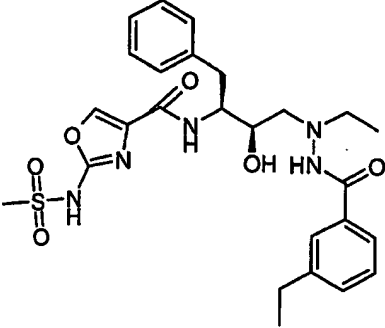
1322	 <p>3-(Benzothiazol-2-ylamino)-4-(3,5-difluorophenyl)-1-(3-methoxybenzylamino)-butan-2-ol</p>
1323	 <p>4-(3,5-Difluorophenyl)-1-(3-methoxybenzylamino)-3-(2-phenylquinolin-4-ylamino)-butan-2-ol</p>
1324	 <p>6-[1-(3,5-Difluorobenzyl)-2-hydroxy-3-(3-methoxybenzylamino)-propylamino]-nicotinonitrile</p>
1325	 <p>2-[1-(3,5-Difluorobenzyl)-2-hydroxy-3-(3-methoxybenzylamino)-propylamino]-nicotinic acid ethyl ester</p>
1326	 <p>4-(3,5-Difluorophenyl)-1-(3-methoxybenzylamino)-3-(3-methyl-5-nitro-3H-imidazol-4-ylamino)-butan-2-ol</p>

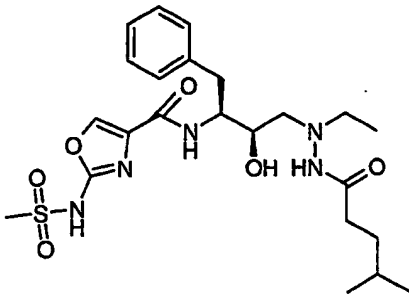
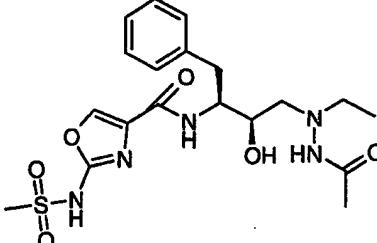
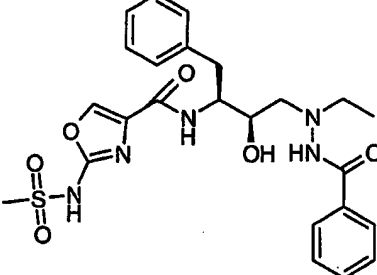
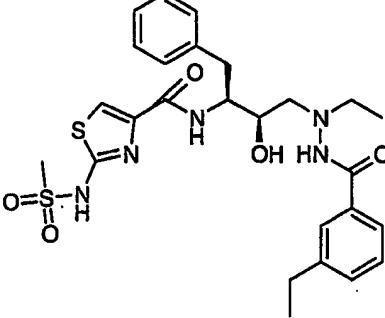
	ylamino)-butan-2-ol
1327	 <p>3-(Benzooxazol-2-ylamino)-4-(3,5-difluoro-phenyl)-1-(3-methoxy-benzylamino)-butan-2-ol</p>
1328	 <p>4-(3,5-Difluoro-phenyl)-1-(3-methoxy-benzylamino)-3-(quinolin-4-ylamino)-butan-2-ol</p>
1329	 <p>4-(3,5-Difluoro-phenyl)-3-(5-ethyl-pyrimidin-2-ylamino)-1-(3-methoxy-benzylamino)-butan-2-ol</p>
1330	 <p>4-(3,5-Difluoro-phenyl)-1-(3-methoxy-benzylamino)-3-(4-trifluoromethyl-pyrimidin-2-ylamino)-butan-2-ol</p>
1331	 <p>3-(6-Chloro-2-methylsulfanyl-5-phenyl-pyrimidin-4-ylamino)-4-(3,5-difluoro-phenyl)-1-(3-methoxy-benzylamino)-butan-2-ol</p>

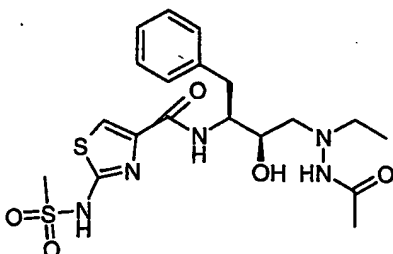
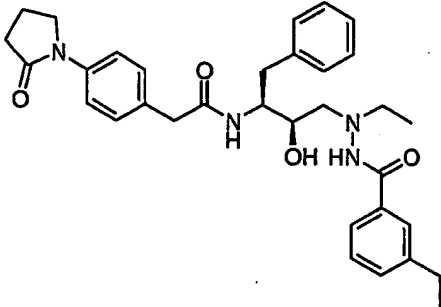
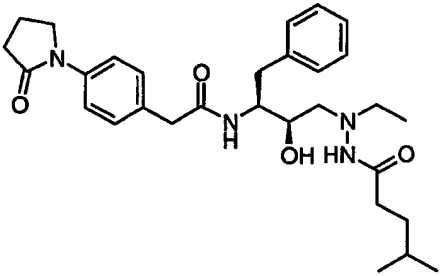
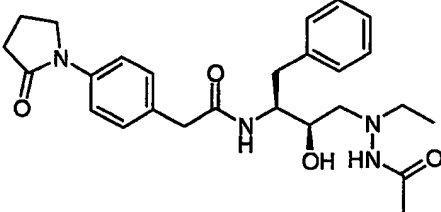


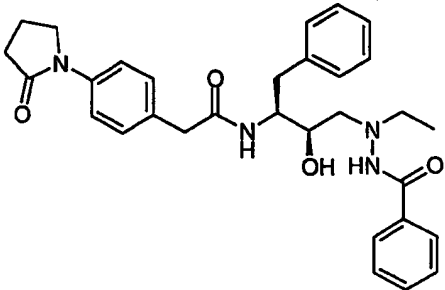
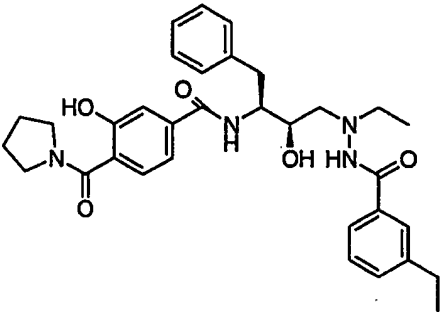
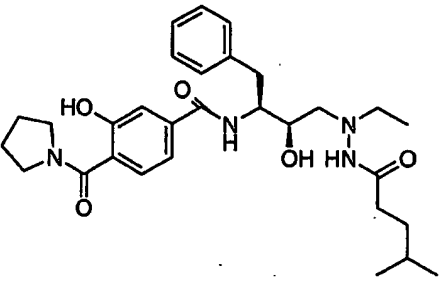
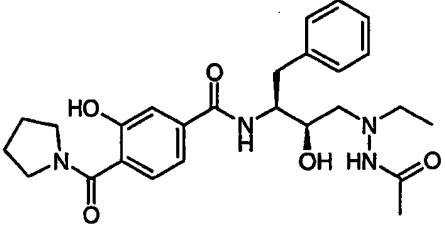
1332	 <p>3-(3-Chloro-quinoxalin-2-ylamino)-4-(3,5-difluoro-phenyl)-1-(3-methoxy-benzylamino)-butan-2-ol</p>
1333	 <p>4-(3,5-Difluoro-phenyl)-1-(3-methoxy-benzylamino)-3-(8-trifluoromethyl-quinolin-4-ylamino)-butan-2-ol</p>
1334	 <p>3-(6-Chloro-2,5-diphenyl-pyrimidin-4-ylamino)-4-(3,5-difluoro-phenyl)-1-(3-methoxy-benzylamino)-butan-2-ol</p>
1335	 <p>3-(3-Chloro-pyrazin-2-ylamino)-4-(3,5-difluoro-phenyl)-1-(3-methoxy-benzylamino)-butan-2-ol</p>
1336	 <p>4-(3,5-Difluoro-phenyl)-1-(3-methoxy-benzylamino)-3-(5-trifluoromethyl-pyridin-2-ylamino)-butan-2-ol</p>

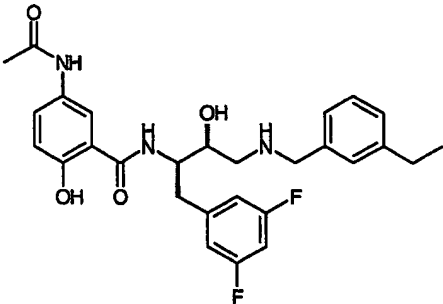
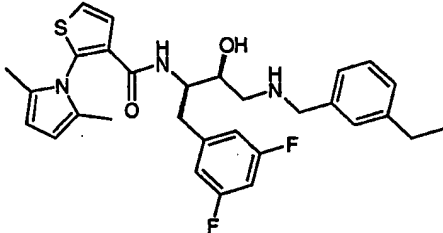
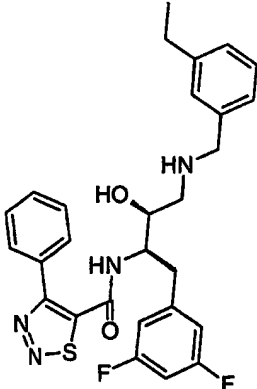
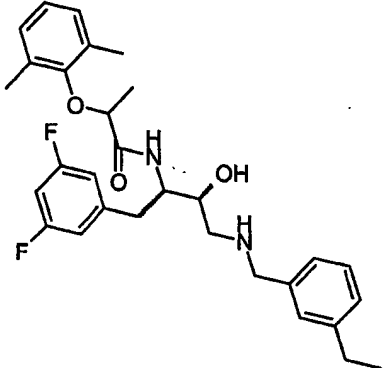
1337	 <p>4-(3,5-Difluoro-phenyl)-1-(3-methoxy-benzylamino)-3-(quinolin-2-ylamino)-butan-2-ol</p>
1338	 <p>3-(6-Chloro-pyrazin-2-ylamino)-4-(3,5-difluoro-phenyl)-1-(3-methoxy-benzylamino)-butan-2-ol</p>
1339	 <p>4-(3,5-Difluoro-phenyl)-1-(3-methoxy-benzylamino)-3-(3-nitro-pyridin-2-ylamino)-butan-2-ol</p>
1340	 <p>4-(3,5-Difluoro-phenyl)-1-(3-methoxy-benzylamino)-3-(pyrimidin-2-ylamino)-butan-2-ol</p>
1341	 <p>4-(3,5-Difluoro-phenyl)-1-(3-methoxy-benzylamino)-3-(2-phenyl-quinazolin-4-ylamino)-butan-2-ol</p>

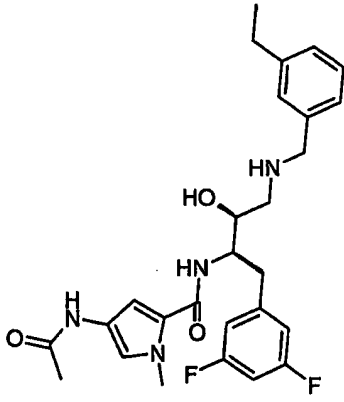
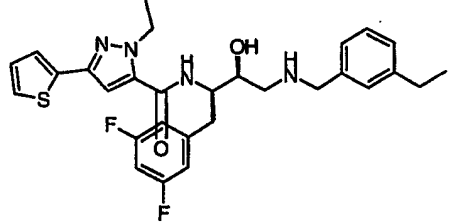
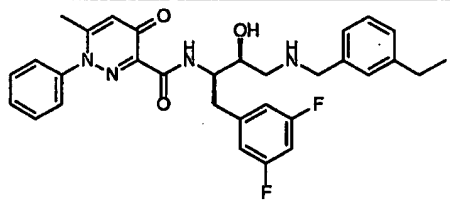
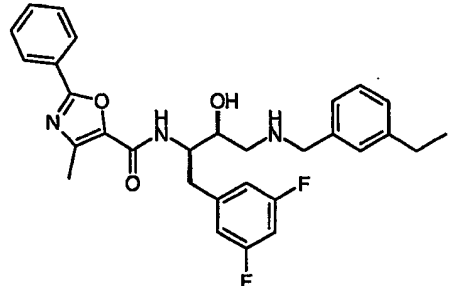
1342	 <p>3-(4,6-Diamino-[1,3,5]triazin-2-ylamino)-4-(3,5-difluoro-phenyl)-1-(3-methoxy-benzylamino)-butan-2-ol</p>
1343	 <p>N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[3-(3-hydroxymethyl-piperidine-1-carbonyl)-phenylamino]-propyl}-5-methyl-N',N'-dipropyl-isophthalamide</p>
1344	 <p>N-[3-(3-Cyclohexyl-1-phenyl-propylamino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-5-methyl-N',N'-dipropyl-isophthalamide</p>
1345	 <p>2-Methanesulfonylamino-oxazole-4-carboxylic acid {1-benzyl-3-[N-ethyl-N'-(3-ethyl-benzoyl)-hydrazino]-2-hydroxy-propyl}-amide</p>

1346	 <p>2-Methanesulfonylamino-oxazole-4-carboxylic acid {1-benzyl-3-[N-ethyl-N'-(4-methyl-pentanoyl)- hydrazino]-2-hydroxy-propyl}-amide</p>
1347	 <p>2-Methanesulfonylamino-oxazole-4-carboxylic acid [3-(N'-acetyl-N-ethyl-hydrazino)-1-benzyl-2- hydroxy-propyl]-amide</p>
1348	 <p>2-Methanesulfonylamino-oxazole-4-carboxylic acid [3-(N'-benzoyl-N-ethyl-hydrazino)-1-benzyl-2- hydroxy-propyl]-amide</p>
1349	 <p>2-Methanesulfonylamino-thiazole-4-carboxylic acid {1-benzyl-3-[N-ethyl-N'-(3-ethyl-benzoyl)- hydrazino]-2-hydroxy-propyl}-amide</p>

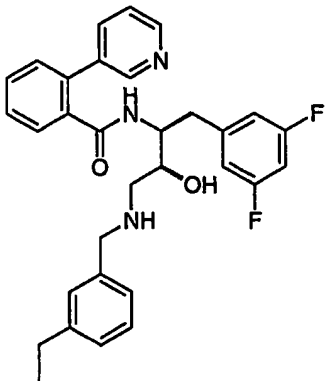
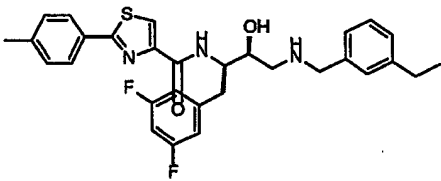
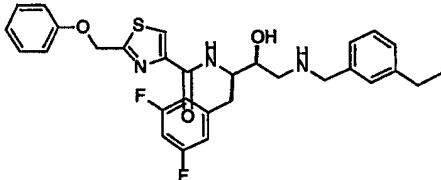
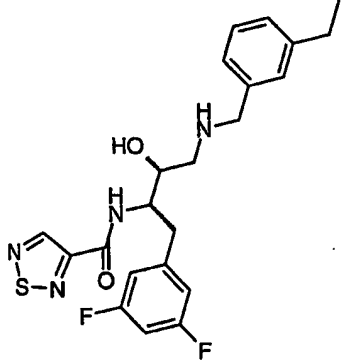
1350	 <p>2-Methanesulfonylamino-thiazole-4-carboxylic acid [3-(N'-acetyl-N-ethyl-hydrazino)-1-benzyl-2-hydroxy-propyl]-amide</p>
1351	 <p>N-{1-Benzyl-3-[N-ethyl-N'-(3-ethyl-benzoyl)-hydrazino]-2-hydroxy-propyl}-2-[4-(2-oxo-pyrrolidin-1-yl)-phenyl]-acetamide</p>
1352	 <p>N-{1-Benzyl-3-[N-ethyl-N'-(4-methyl-pentanoyl)-hydrazino]-2-hydroxy-propyl}-2-[4-(2-oxo-pyrrolidin-1-yl)-phenyl]-acetamide</p>
1353	 <p>N-[3-(N'-Acetyl-N-ethyl-hydrazino)-1-benzyl-2-hydroxy-propyl]-2-[4-(2-oxo-pyrrolidin-1-yl)-phenyl]-acetamide</p>

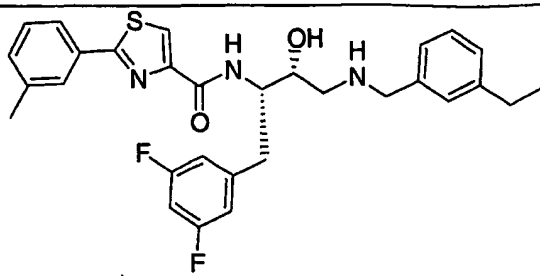
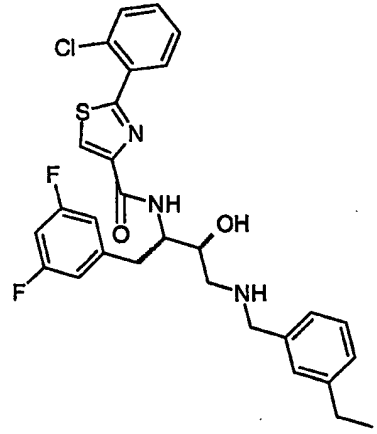
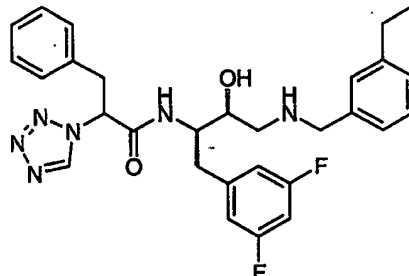
1354	 <p>N-[3-(N'-Benzoyl-N-ethyl-hydrazino)-1-benzyl-2-hydroxy-propyl]-2-[4-(2-oxo-pyrrolidin-1-yl)-phenyl]-acetamide</p>
1355	 <p>N-{1-Benzyl-3-[N-ethyl-N'-(3-ethyl-benzoyl)-hydrazino]-2-hydroxy-propyl}-3-hydroxy-4-(pyrrolidine-1-carbonyl)-benzamide</p>
1356	 <p>N-{1-Benzyl-3-[N-ethyl-N'-(4-methyl-pentanoyl)-hydrazino]-2-hydroxy-propyl}-3-hydroxy-4-(pyrrolidine-1-carbonyl)-benzamide</p>
1341	 <p>N-[3-(N'-Acetyl-N-ethyl-hydrazino)-1-benzyl-2-hydroxy-propyl]-3-hydroxy-4-(pyrrolidine-1-carbonyl)-benzamide</p>

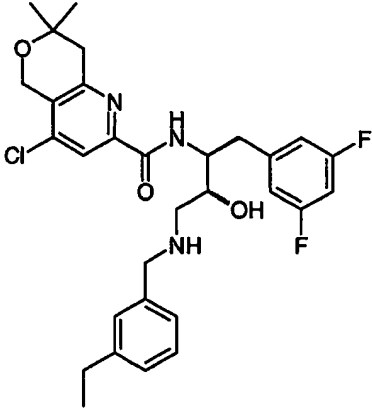
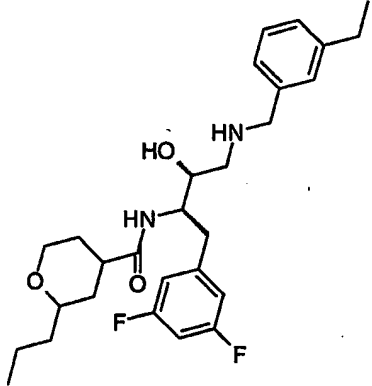
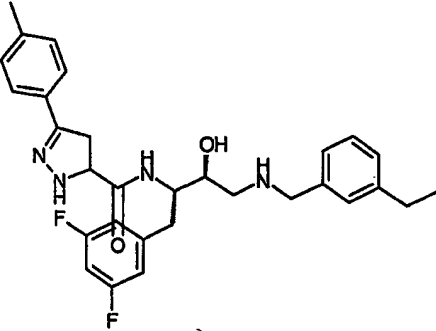
1342	 <p>5-Acetylamino-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-hydroxy-benzamide</p>
1343	 <p>2-(2,5-Dimethyl-pyrrol-1-yl)-thiophene-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1344	 <p>4-Phenyl-[1,2,3]thiadiazole-5-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1345	

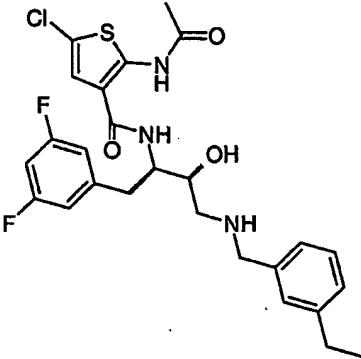
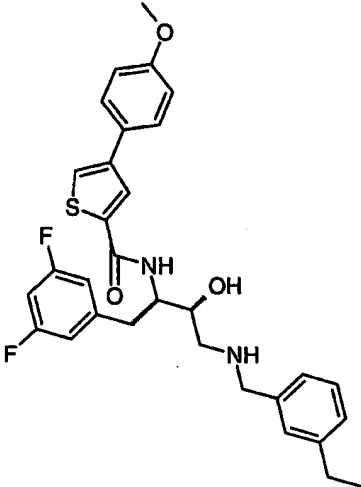
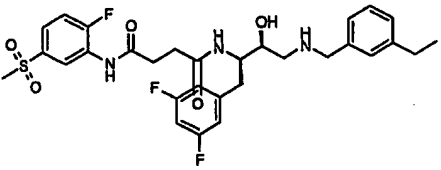
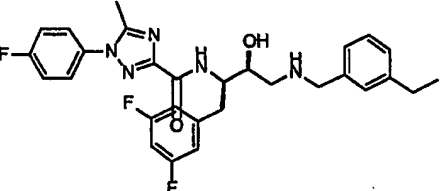
	N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-(2,6-dimethyl-phenoxy)-propionamide
1346	 <p>4-Acetyl-1-methyl-1H-pyrrole-2-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1347	 <p>2-Ethyl-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1348	 <p>6-Methyl-4-oxo-1-phenyl-1,4-dihydro-pyridazine-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1349	 <p>4-Methyl-2-phenyl-oxazole-5-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>

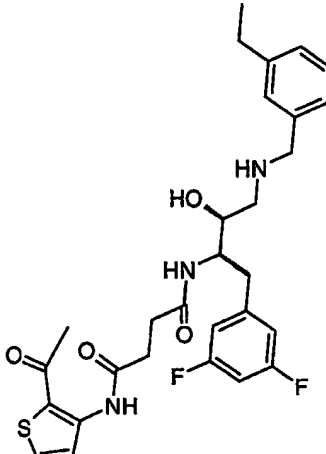
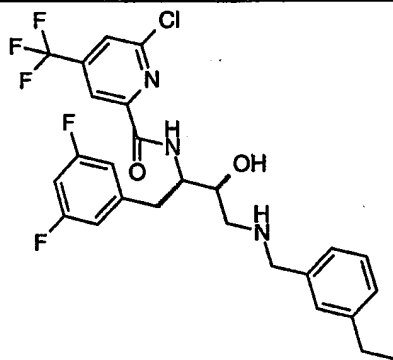
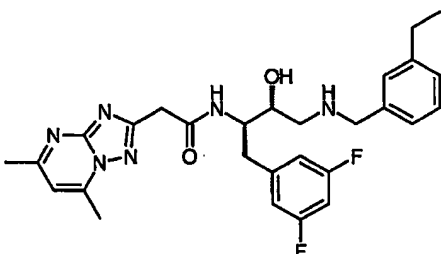


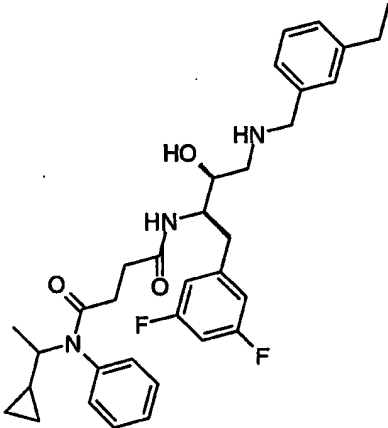
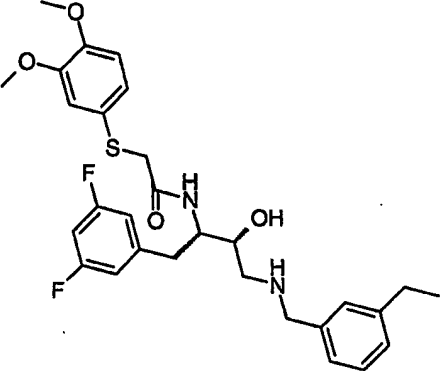
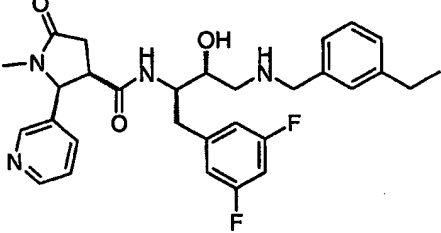
1350	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-pyridin-3-yl-benzamide</p>
1351	 <p>2-p-Tolyl-thiazole-4-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1352	 <p>2-Phenoxymethyl-thiazole-4-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1353	 <p>[1,2,5]Thiadiazole-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>

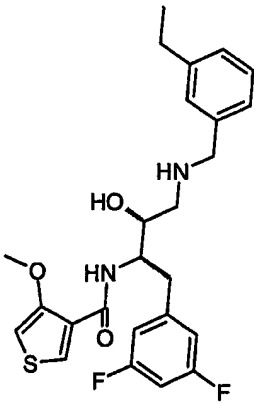
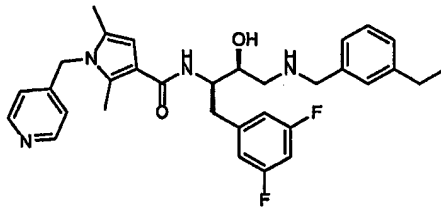
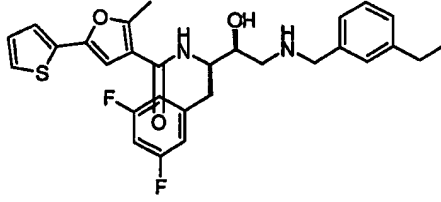
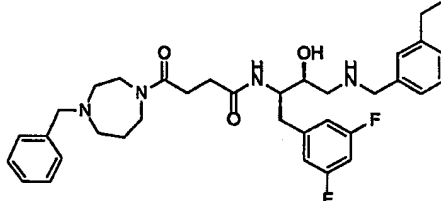
1354	 <p>2-m-Tolyl-thiazole-4-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1355	 <p>2-(2-Chloro-phenyl)-thiazole-4-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1356	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-3-phenyl-2-tetrazol-1-yl-propionamide</p>

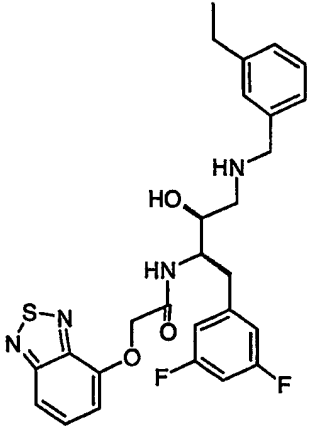
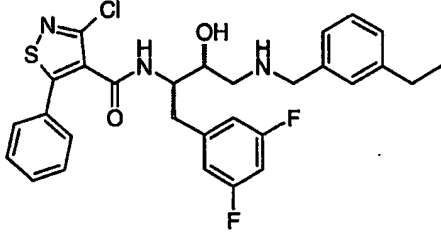
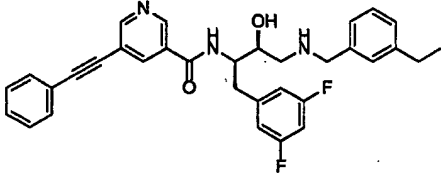
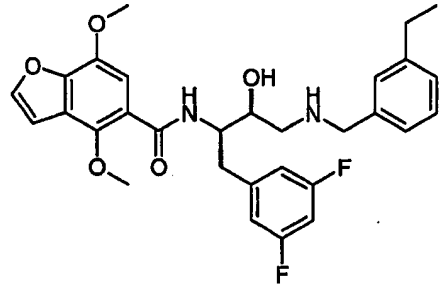
1357	 <p>4-Chloro-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-b]pyridine-2-carboxylic acid [1-(3,5-difluorobenzyl)-3-(3-ethylbenzylamino)-2-hydroxypropyl]-amide</p>
1358	 <p>2-Propyl-tetrahydro-pyran-4-carboxylic acid [1-(3,5-difluorobenzyl)-3-(3-ethylbenzylamino)-2-hydroxypropyl]-amide</p>
1359	 <p>5-p-Tolyl-3,4-dihydro-2H-pyrazole-3-carboxylic acid [1-(3,5-difluorobenzyl)-3-(3-ethylbenzylamino)-2-hydroxypropyl]-amide</p>

1360	 <p>2-Acetyl-5-chloro-thiophene-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1361	 <p>4-(4-Methoxy-phenyl)-thiophene-2-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1362	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-N'-(2-fluoro-5-methanesulfonyl-phenyl)-succinamide</p>
1363	 <p>1-(4-Fluoro-phenyl)-5-methyl-1H-[1,2,4]triazole-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>

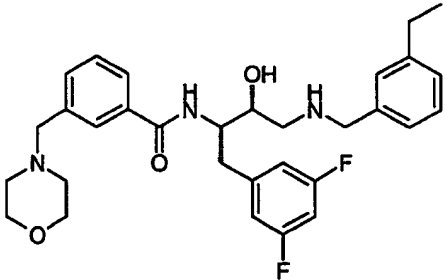
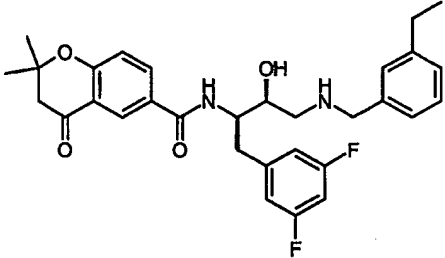
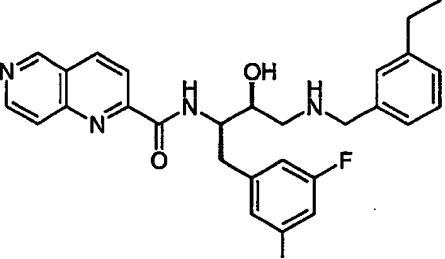
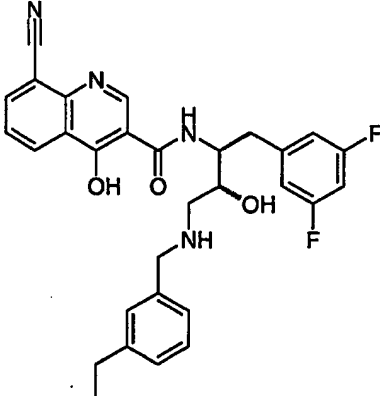
	ethyl-benzylamino)-2-hydroxy-propyl]-amide
1364	 <p>N-(2-Acetyl-thiophen-3-yl)-N'-[1-(3,5-difluorobenzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-succinamide</p>
1365	 <p>6-Chloro-4-trifluoromethyl-pyridine-2-carboxylic acid [1-(3,5-difluorobenzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1366	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-acetamide</p>

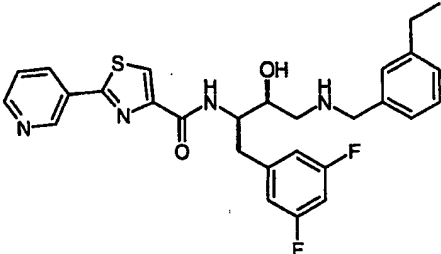
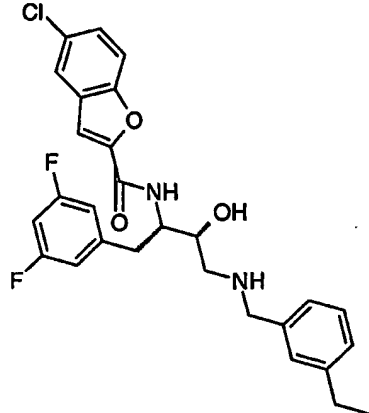
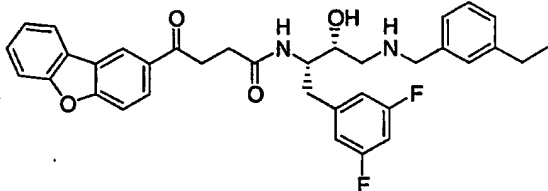
1367	 <p>N-(1-Cyclopropyl-ethyl)-N'-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-N-phenyl-succinamide</p>
1368	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-(3,4-dimethoxy-phenylsulfanyl)-acetamide</p>
1369	 <p>1-Methyl-5-oxo-2-pyridin-3-yl-pyrrolidine-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>

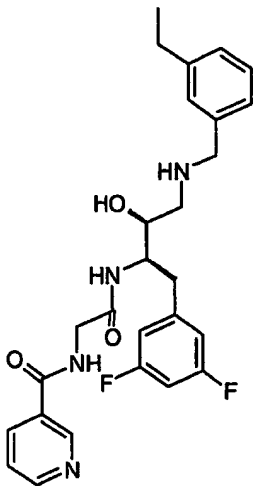
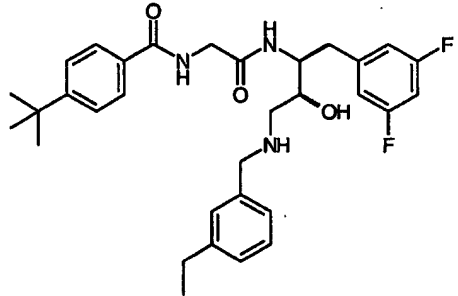
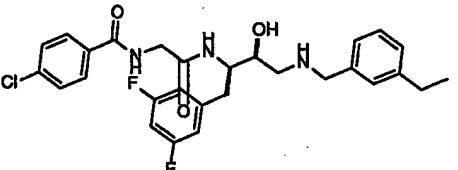
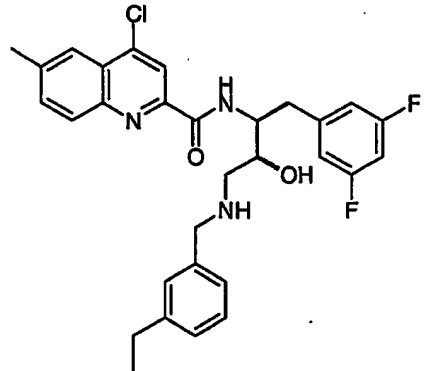
1370	 <p>4-Methoxy-thiophene-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1371	 <p>2,5-Dimethyl-1-pyridin-4-ylmethyl-1H-pyrrole-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1372	 <p>2-Methyl-5-thiophen-2-yl-furan-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1373	 <p>4-(4-Benzyl-[1,4]diazepan-1-yl)-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-4-oxo-butyramide</p>

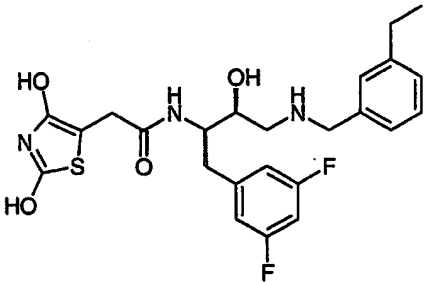
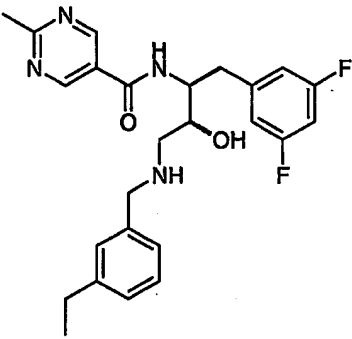
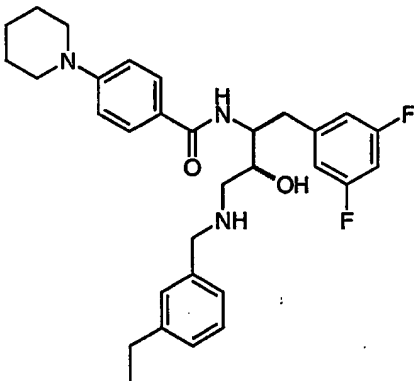
1374	 <p>2-(Benzo[1,2,5]thiadiazol-4-yloxy)-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-acetamide</p>
1375	 <p>3-Chloro-5-phenyl-isothiazole-4-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1376	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-5-phenylethynyl-nicotinamide</p>
1377	 <p>4,7-Dimethoxy-benzofuran-5-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>

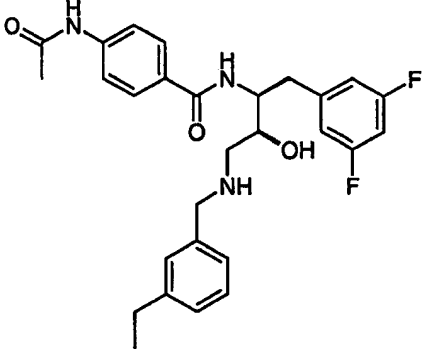
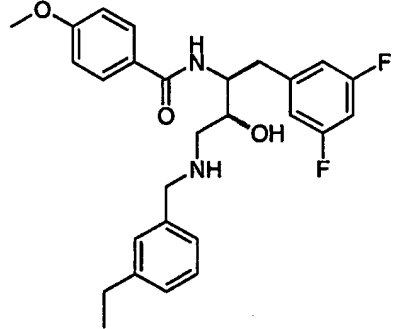
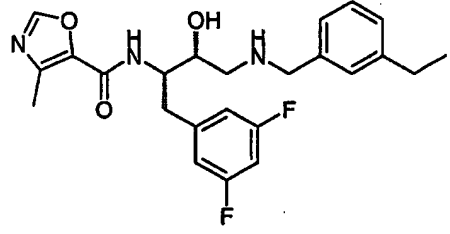
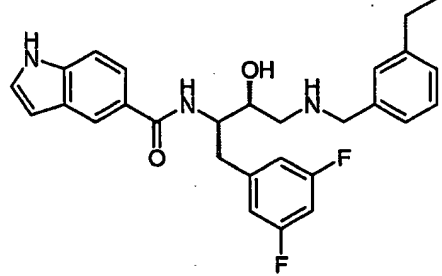


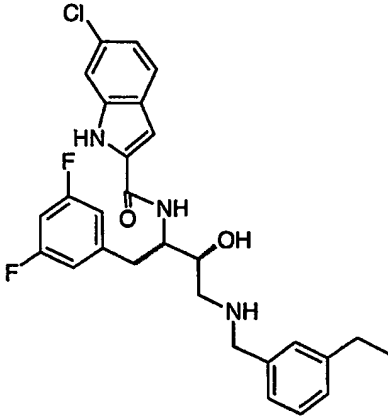
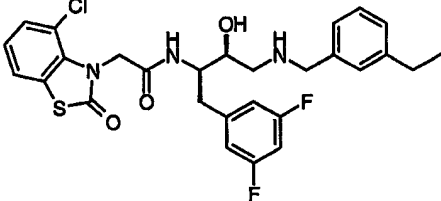
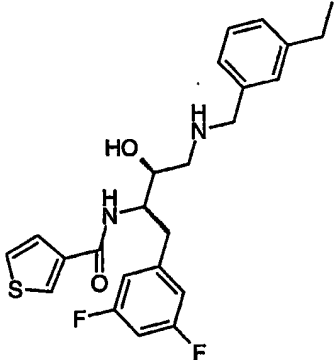
1378	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-3-morpholin-4-ylmethyl-benzamide</p>
1379	 <p>2,2-Dimethyl-4-oxo-chroman-6-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1380	 <p>[1,6]Naphthyridine-2-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1381	 <p>8-Cyano-4-hydroxy-quinoline-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>

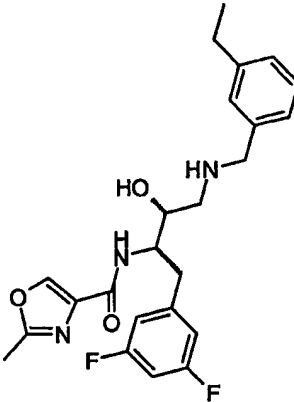
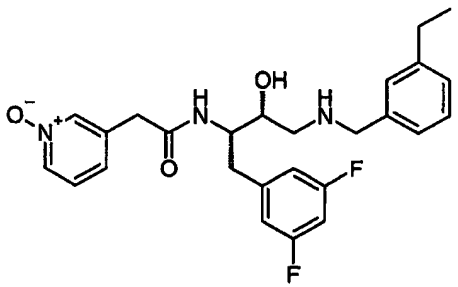
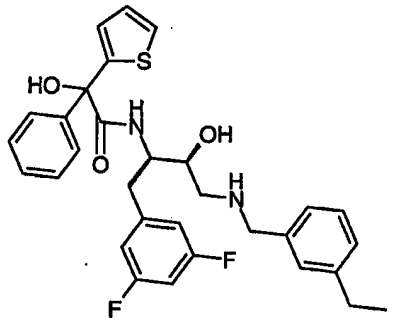
	benzylamino)-2-hydroxy-propyl]-amide
1382	 <p>2-Pyridin-3-yl-thiazole-4-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1383	 <p>5-Chloro-benzofuran-2-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1384	 <p>4-Dibenzofuran-2-yl-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-4-oxo-butyramide</p>

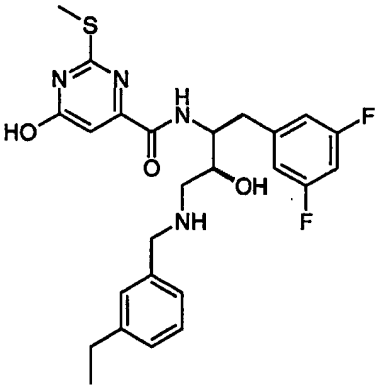
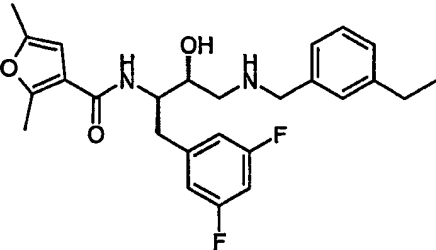
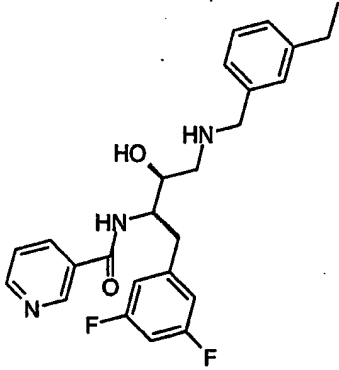
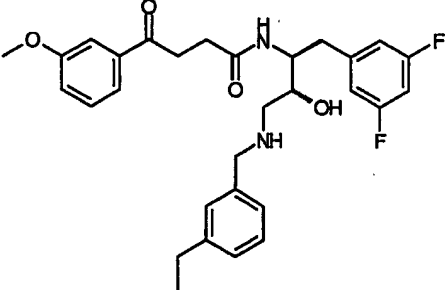
1385	 <p>N-{[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylcarbamoyl]-methyl}-nicotinamide</p>
1386	 <p>4-tert-Butyl-N-{[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylcarbamoyl]-methyl}-benzamide</p>
1387	 <p>4-Chloro-N-{[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propylcarbamoyl]-methyl}-benzamide</p>
1388	

	4-Chloro-6-methyl-quinoline-2-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl- benzylamino)-2-hydroxy-propyl]-amide
1389	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl- benzylamino)-2-hydroxy-propyl]-2-(2,4-dihydroxy- thiazol-5-yl)-acetamide</p>
1390	 <p>2-Methyl-pyrimidine-5-carboxylic acid [1-(3,5- difluoro-benzyl)-3-(3-ethyl-benzylamino)-2- hydroxy-propyl]-amide</p>
1391	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl- benzylamino)-2-hydroxy-propyl]-4-piperidin-1-yl- benzamide</p>

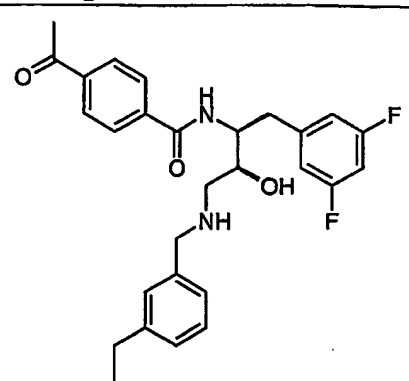
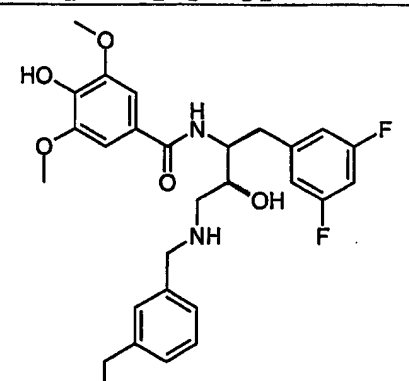
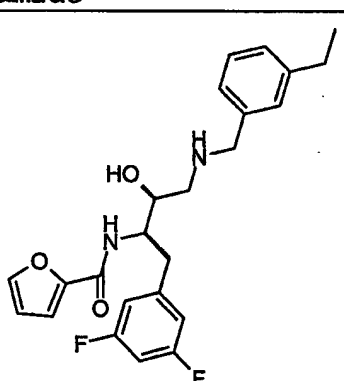
1392	 <p>4-Acetylamino-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-benzamide</p>
1393	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-4-methoxy-benzamide</p>
1394	 <p>4-Methyl-oxazole-5-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1395	 <p>1H-Indole-5-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>

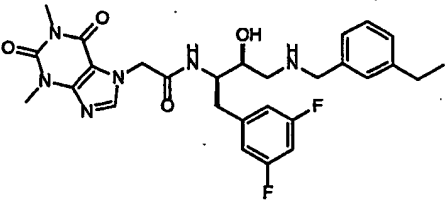
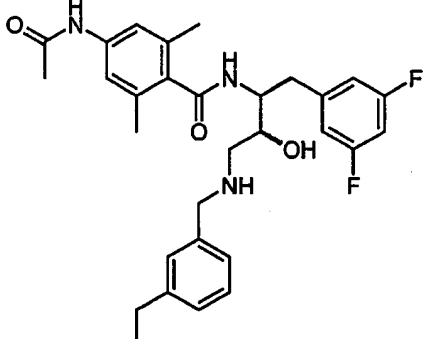
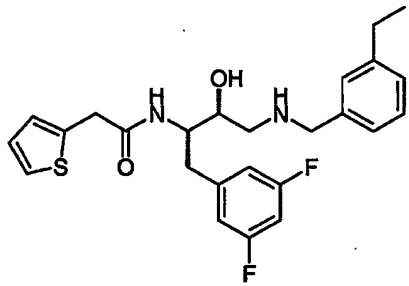
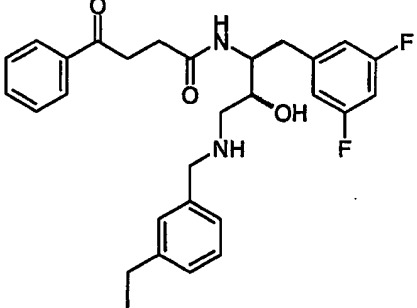
1396	 <p>6-Chloro-1H-indole-2-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1397	 <p>2-(4-Chloro-2-oxo-benzothiazol-3-yl)-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-acetamide</p>
1398	 <p>Thiophene-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>

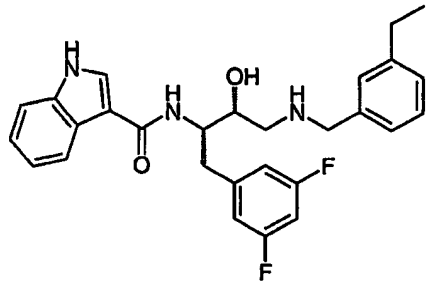
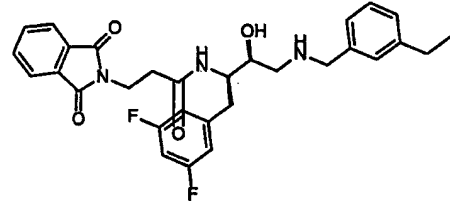
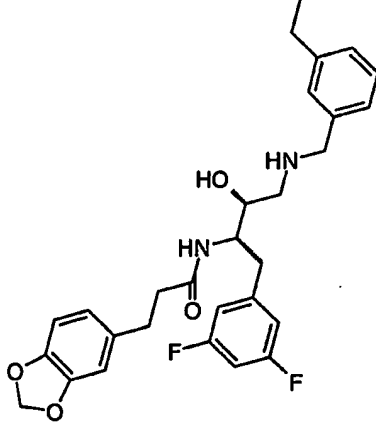
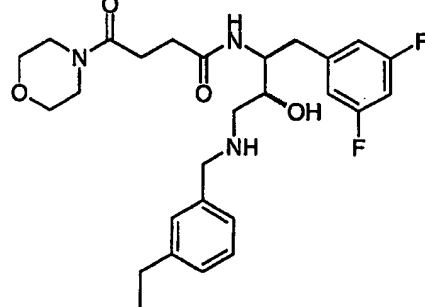
1399	 <p>2-Methyl-oxazole-4-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1400	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-(1-oxy-pyridin-3-yl)-acetamide</p>
1401	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-hydroxy-2-phenyl-2-thiophen-2-yl-acetamide</p>

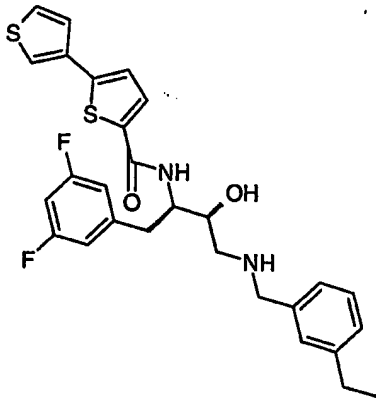
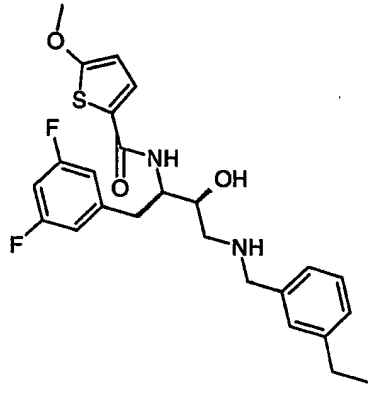
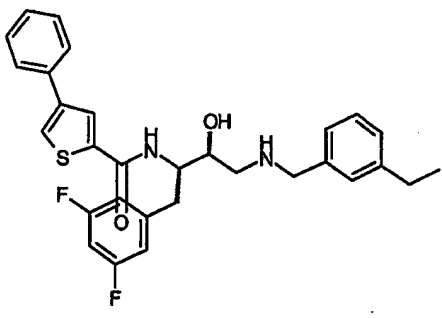
1402	 <p>6-Hydroxy-2-methylsulfanyl-pyrimidine-4-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1403	 <p>2,5-Dimethyl-furan-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1404	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-nicotinamide</p>
1405	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-4-methoxybenzamide</p>

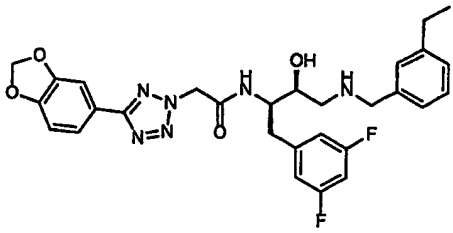
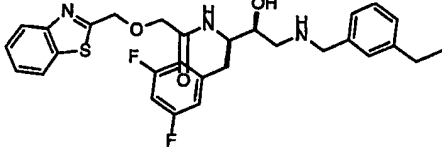
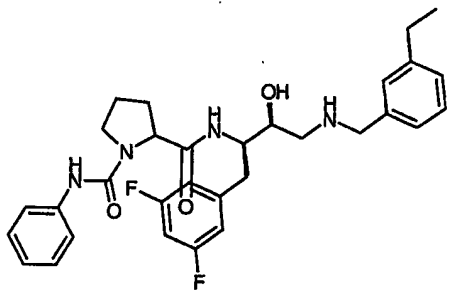
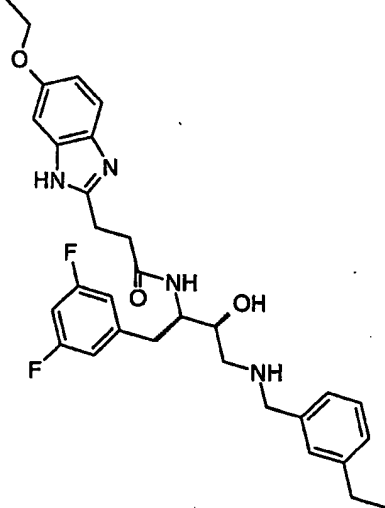


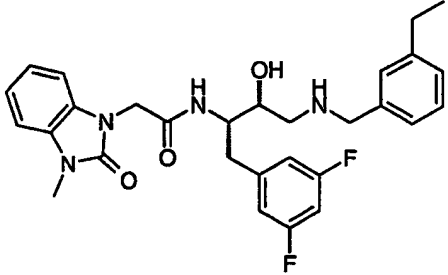
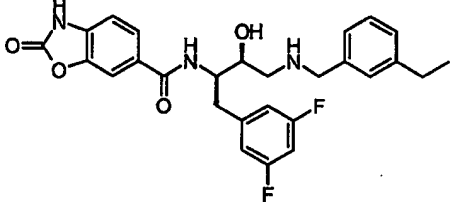
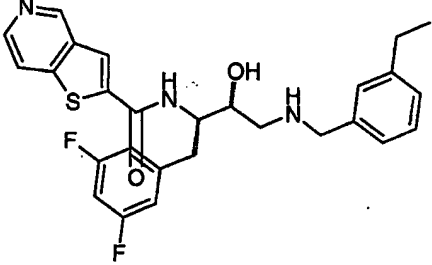
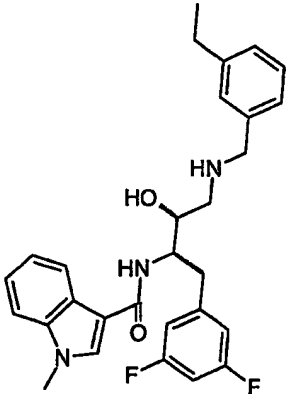
	benzylamino)-2-hydroxy-propyl]-4-(3-methoxy-phenyl)-4-oxo-butyramide
1406	 <p>4-Acetyl-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-benzamide</p>
1407	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-4-hydroxy-3,5-dimethoxy-benzamide</p>
1408	 <p>Furan-2-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>

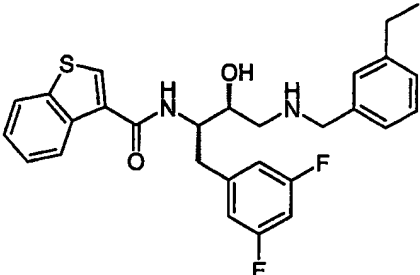
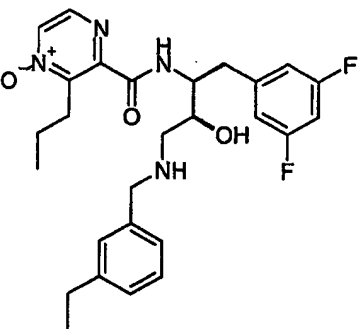
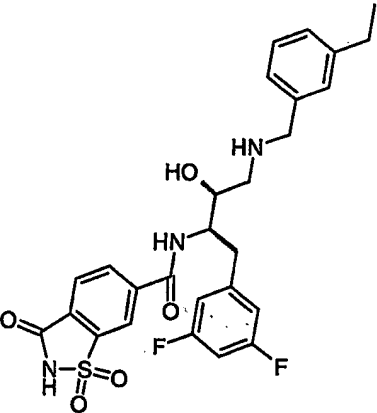
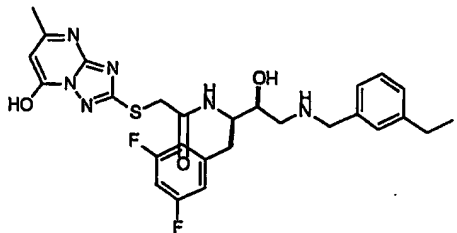
1409	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl)-acetamide</p>
1410	 <p>4-Acetylamino-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2,6-dimethyl-benzamide</p>
1411	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-thiophen-2-yl-acetamide</p>
1412	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-4-oxo-4-phenyl-butamide</p>

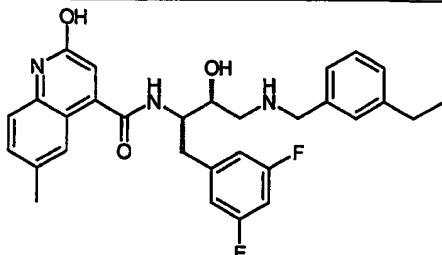
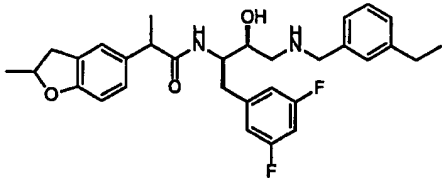
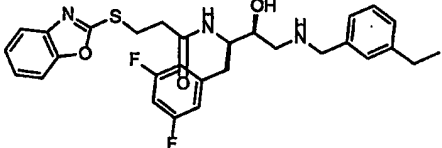
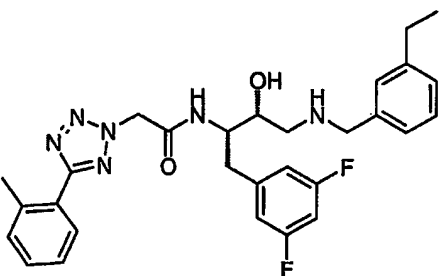
1413	 <p>1H-Indole-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1414	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionamide</p>
1415	 <p>3-Benzo[1,3]dioxol-5-yl-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-propionamide</p>
1416	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-4-morpholin-4-yl-propionamide</p>

	4-oxo-butyramide
1417	 <p>[2,3']Bithiophenyl-5-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1418	 <p>5-Methoxy-thiophene-2-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1419	 <p>4-Phenyl-thiophene-2-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>

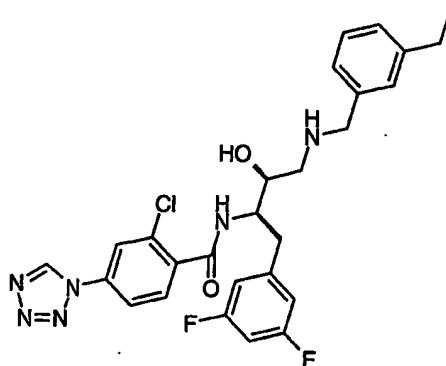
1420	 <p>2-(5-Benzo[1,3]dioxol-5-yl-tetrazol-2-yl)-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-acetamide</p>
1421	 <p>2-(Benzothiazol-2-ylmethoxy)-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-acetamide</p>
1422	 <p>Pyrrolidine-1,2-dicarboxylic acid 1-([1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide) 2-phenylamide</p>
1423	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-3-(6-ethoxy-1H-benzoimidazol-2-yl)-propionamide</p>

1424	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-(3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-acetamide</p>
1425	 <p>2-Oxo-2,3-dihydro-benzooxazole-6-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1426	 <p>Thieno[3,2-c]pyridine-2-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1427	 <p>1-Methyl-1H-indole-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>

1428	 <p>Benzo[b]thiophene-3-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1429	 <p>4-Oxy-3-propyl-pyrazine-2-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1430	 <p>1,1,3-Trioxo-2,3-dihydro-1H-116-benzo[d]isothiazole-6-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1431	

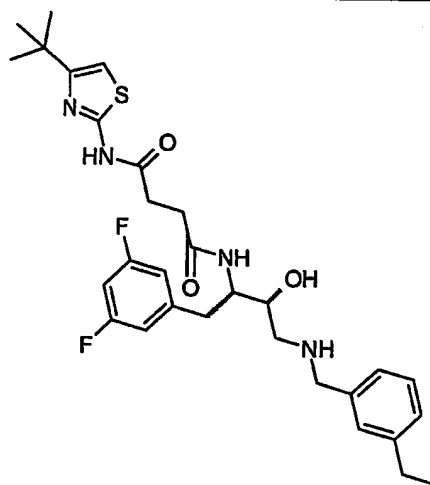
	N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-(7-hydroxy-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylsulfanyl)-acetamide
1432	 <p>2-Hydroxy-6-methyl-quinoline-4-carboxylic acid [1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-amide</p>
1433	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-(2-methyl-2,3-dihydro-benzofuran-5-yl)-propionamide</p>
1434	 <p>3-(Benzooxazol-2-ylsulfanyl)-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-propionamide</p>
1435	 <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-2-(5-o-tolyl-tetrazol-2-yl)-acetamide</p>





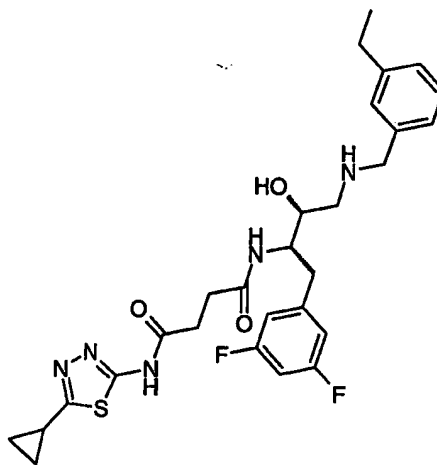
1436

2-Chloro-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-4-tetrazol-1-yl-benzamide



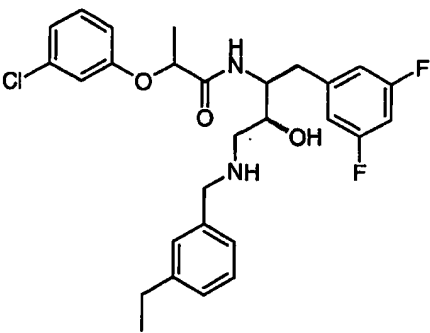
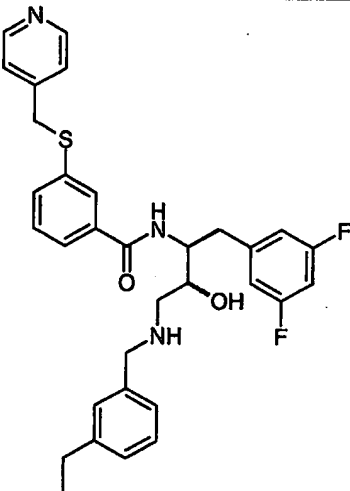
1437

N-(4-tert-Butyl-thiazol-2-yl)-N'-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-succinamide



1438

N-(5-Cyclopropyl-[1,3,4]thiadiazol-2-yl)-N'-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-succinamide

	hydroxy-propyl]-succinamide
1439	<div></div> <p>2-(3-Chloro-phenoxy)-N-[1-(3,5-difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-propionamide</p>
1440	<div></div> <p>N-[1-(3,5-Difluoro-benzyl)-3-(3-ethyl-benzylamino)-2-hydroxy-propyl]-3-(pyridin-4-ylmethylsulfanyl)-benzamide</p>

The compounds in the table immediately below were prepared essentially using the methods described above and illustrated below in the schemes.

The following compounds were named using the Advanced  
 5 Chemistry Development Inc. (ACD) nomenclature program, IUPAC  
 Name Batch Version 4.5. The website for ACD is  
 www.acdlabs.com.

	Compound Name (IUPAC Name)
1441	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(2-hydroxyethyl)amino]sulfonyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1442	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-isobutyl-1,3-thiazol-5-yl)methyl]amino}propyl)-5-ethynyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1443	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-5-ethynyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1444	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1445	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1446	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(4-methyl-1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1447	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-isobutyl-1,3-thiazol-5-yl)methyl]amino}propyl)-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1448	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(3-hydroxypropyl)amino]sulfonyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1449	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-propylbenzyl)amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1451	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-5-ethynyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1452	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isobutylisoxazol-5-

	yl)methyl]amino}propyl)-5-ethynyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1453	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(dimethylamino)sulfonyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1454	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide hydrochloride
1455	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1456	5-bromo-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1457	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-({[(1R)-2-hydroxy-1-methylethyl]amino}sulfonyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1458	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isobutylbenzyl)amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1459	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-(trifluoromethyl)benzyl)amino]propyl)-5-ethynyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1460	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-({[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride
1461	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-({[(1S)-2-hydroxy-1-methylethyl]amino}sulfonyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1462	N <sup>1</sup> -butyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>1</sup> -propylisophthalamide
1463	N <sup>1</sup> ,N <sup>1</sup> -dibutyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisophthalamide
1464	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-(3-hydroxyprop-1-ynyl)benzyl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1465	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-({[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]sulfonyl}-

	N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1467	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1469	N <sup>1</sup> -[(1S,2R)-3-[(3-(cyclopropylamino)benzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-ethynyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1470	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-thien-3-ylbenzyl)amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1471	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-(trifluoromethyl)benzyl)amino]propyl}-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1472	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(piperazin-1-ylsulfonyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1473	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[1-(3-iodophenyl)cyclopropyl]amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1474	N <sup>1</sup> -[(1S,2R)-3-[(3-sec-butylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1475	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(3-methylisoxazol-4-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide hydrochloride
1476	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[1-(3-isobutylisoxazol-5-yl)cyclopropyl]amino]propyl}-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1477	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1478	N <sup>4</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-methyl-N <sup>2</sup> ,N <sup>2</sup> -dipropylpyridine-2,4-dicarboxamide
1480	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1481	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1482	5-(aminosulfonyl)-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-

	hydroxypropyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1483	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({3-[(1Z)-prop-1-enyl]benzyl}amino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1484	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropyl-5-(1H-pyrazol-4-yl)isophthalamide
1485	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-{{1-(3-ethylphenyl)-1-methylethyl}amino}-2-hydroxypropyl)-5-ethynyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1487	N <sup>1</sup> -[(1S,2R)-3-[(3-allylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1488	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-{{1-(3-ethylphenyl)cyclopropyl}amino}-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1489	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-{{1-(3-ethylphenyl)-1-methylethyl}amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1490	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>3</sup> -ethyl-5-methyl-N <sup>3</sup> -propylisophthalamide
1491	N <sup>1</sup> -[(1S,2R)-3-{{3-(cyclopropylamino)benzyl}amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1492	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-{{1-(3-ethynylphenyl)cyclopropyl}amino}-2-hydroxypropyl)-5-ethynyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1493	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{{1-(3-isobutylisoxazol-5-yl)cyclopropyl}amino}propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1494	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-{{3-(5-formyl-4-methylthien-2-yl)benzyl}amino}-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1496	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({3-[(methylsulfonyl)amino]benzyl}amino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1498	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopentylbenzyl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1500	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-{{1-(3-ethynylphenyl)cyclopropyl}amino}-2-

	hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1501	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[[2-(methylamino)ethyl]amino)sulfonyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide dihydrochloride
1502	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[1-(3-isobutylisoxazol-5-yl)cyclopropyl]amino]propyl)-5-ethynyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1504	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[1-(2-isobutyl-1,3-thiazol-5-yl)cyclopropyl]amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1505	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)-1-methylethyl]amino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1506	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[[2-hydroxyethyl]amino)sulfonyl)-N <sup>3</sup> -propylisophthalamide
1507	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,5-dimethyl-N <sup>3</sup> -propylisophthalamide
1508	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -(phenylsulfonyl)-3-[(1-propylbutyl)sulfonyl]alaninamide
1509	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -diethyl-5-(1,3-oxazol-2-yl)isophthalamide
1510	N <sup>2</sup> -[(benzylamino)carbonyl]-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide
1511	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-pyridin-3-ylbenzyl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1512	N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpyridine-3,5-dicarboxamide 1-oxide
1513	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[3-(3-formyl-2-furyl)benzyl]amino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1514	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1-methyl-1H-imidazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide

1515	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -diethyl-5-methylisophthalamide
1516	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-(ethylsulfonyl)benzyl)amino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1517	3-[(butyl(ethyl)amino)sulfonyl]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}propanamide
1519	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]propanamide hydrochloride
1520	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -isobutyl-N <sup>3</sup> ,5-dimethylisophthalamide
1521	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-pyridin-2-ylbenzyl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1523	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-[methyl(methylsulfonyl)amino]benzyl)amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1524	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -(3-phenylpropanoyl)-3-[(1-propylbutyl)sulfonyl]alaninamide trifluoroacetate
1525	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-(ethylsulfonyl)benzyl)amino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1526	N <sup>2</sup> -[(5-chlorothien-2-yl)sulfonyl]-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]alaninamide
1527	N <sup>1</sup> -[(1S,2R)-3-[(3-(5-acetylthien-2-yl)benzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1529	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(1,3-oxazol-2-yl)benzamide hydrochloride
1530	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,5-dimethyl-N <sup>3</sup> -(2-phenylethyl)isophthalamide
1531	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-(3,5-dimethylisoxazol-4-yl)benzyl)amino]-2-



	hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1532	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,5-dimethyl-N <sup>3</sup> -prop-2-ynylisophthalamide
1533	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -ethyl-N <sup>3</sup> ,5-dimethylisophthalamide
1535	N <sup>1</sup> -benzyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>1</sup> ,5-dimethylisophthalamide
1536	N <sup>1</sup> -(sec-butyl)-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>1</sup> -propylisophthalamide
1537	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-(4-methylthien-2-yl)benzyl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1538	methyl 3-({[(2R,3S)-4-(3,5-difluorophenyl)-3-({3-[(dipropylamino)carbonyl]-5-methylbenzoyl}amino)-2-hydroxybutyl]amino}methyl)phenyl(methyl)carbamate
1539	N <sup>1</sup> -{(1S,2R)-2-hydroxy-1-(2,3,5-trifluorobenzyl)-3-[(3-(trifluoromethyl)benzyl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1540	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -diisobutyl-5-methylisophthalamide
1541	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,5-dimethyl-N <sup>3</sup> -(2-pyridin-2-ylethyl)isophthalamide
1542	N <sup>1</sup> -{(1S,2R)-1-(3-fluoro-5-hydroxybenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide hydrochloride
1544	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-4-hydroxy-3-(pyrrolidin-1-ylcarbonyl)benzamide
1545	5-oxo-D-prolyl-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]alaninamide hydrochloride
1546	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(trifluoromethyl)sulfonyl]amino}benzamide

1547	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-pyridin-4-ylbenzyl)amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1549	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1550	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -(phenylacetyl)-3-[(1-propylbutyl)sulfonyl]alaninamide
1552	methyl 3-([(2R,3S)-4-(3,5-difluorophenyl)-3-({3-[(dipropylamino)carbonyl]-5-methylbenzoyl)amino)-2-hydroxybutyl]amino)methyl phenylcarbamate
1553	5-oxo-L-prolyl-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide hydrochloride
1554	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -isobutyl-5-methylisophthalamide
1555	4-([(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)-4-oxo-3-[(1-propylbutyl)sulfonyl)methyl]butanoic acid trifluoroacetate
1556	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[methyl(methylsulfonyl)amino]benzamide
1557	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -ethyl-N <sup>3</sup> -isopropyl-5-methylisophthalamide
1558	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(thien-2-ylmethyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1559	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2-hydroxyethyl)(propyl)amino]sulfonylpropanamide
1560	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -isopropyl-N <sup>3</sup> ,5-dimethylisophthalamide
1561	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(methylsulfonyl)amino]-1,3-thiazole-4-carboxamide
1562	N <sup>1</sup> -allyl-N <sup>1</sup> -cyclopentyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-

	difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methylisophthalamide
1563	N-(3-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)-3-oxo-2-[[1-(propylbutyl)sulfonyl)methyl]propyl)benzamide
1564	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(isopentylsulfonyl)propanamide
1565	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(5-methylthien-2-yl)benzyl]amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1567	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1-methylhexyl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1568	N <sup>1</sup> -[(1S,2R)-3-[[1-(aminocarbonyl)cyclohexyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1569	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(2E)-hex-2-enylamino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1571	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-hydroxyisoxazole-5-carboxamide
1572	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-[(1E)-hex-1-enyl]benzyl)amino]-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1573	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>3</sup> -isopropyl-5-methylisophthalamide
1574	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(thien-2-ylmethyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1575	2-[3-(2-amino-2-oxoethoxy)phenyl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)acetamide
1576	N <sup>1</sup> -((1S,2R)-1-(3-bromobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1577	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethylhexyl)amino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1578	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(6-methoxypyridin-3-yl)benzyl]amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide

1579	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[[3-(2,4-dimethoxypyrimidin-5-yl)benzyl]amino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1580	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(2-ethylbutanoyl)benzamide
1581	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(4-hydroxypiperidin-1-yl)carbonyl]-5-methylbenzamide
1582	N <sup>1</sup> -((1S,2R)-1-(3-bromobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1583	4'-[4-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)amino]-4-oxobutanoyl]-1,1'-biphenyl-2-carboxamide
1585	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(3-hydroxypiperidin-1-yl)carbonyl]-5-methylbenzamide
1586	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-hydroxy-1-phenylpropyl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1587	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>3</sup> -[2-(dimethylamino)ethyl]-N <sup>3</sup> -ethyl-5-methylisophthalamide
1588	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepine-4-carboxamide
1589	2-(5-acetylthien-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide
1591	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>3</sup> ,N <sup>3</sup> -diisopropyl-5-methylisophthalamide
1592	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(methylsulfonyl)amino]benzamide
1594	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-2-[4-(2-oxopyrrolidin-1-yl)phenyl]acetamide
1595	N-((1S,2R)-1-(3-chloro-5-fluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-[(dipropylamino)sulfonyl]propanamide
1596	N <sup>1</sup> -[(1S,2R)-1-(3-chloro-5-fluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide

1597	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-methyl-1H-imidazol-4-yl)sulfonyl]amino}benzamide trihydrochloride
1598	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(pentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1599	N <sup>1</sup> -[(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1600	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3-chloro-5-fluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1601	N <sup>1</sup> -cyclohexyl-N <sup>3</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N <sup>1</sup> -ethyl-5-methylisophthalamide
1602	2-[(2R,3S)-4-(3,5-difluorophenyl)-3-[(3-(dipropylamino)carbonyl]-5-methylbenzoyl)amino]-2-hydroxybutyl]amino}ethyl difluorophenylcarbamate 2,4-
1603	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl]-5-methylbenzamide hydrochloride
1605	N <sup>1</sup> -[(1S,2R)-1-(3-bromobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1606	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2,8-dimethylquinoline-3-carboxamide
1607	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-hydroxyhexyl)amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1608	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2R)-2-hydroxypropyl]amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1609	N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-[(1-propylbutyl)sulfonyl]propanamide
1610	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}benzamide
1611	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(4-phenylbutyl)amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1612	N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]-7-(1H-imidazol-1-yl)-5,6-dihydronaphthalene-2-

	carboxamide
1613	3-(acetyl amino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-4-methylbenzamide
1614	N <sup>1</sup> -[(1S,2R)-3-([2-(aminosulfonyl) ethyl] amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1615	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-([2-(ethylthio) ethyl] amino)-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1617	N <sup>1</sup> -[(1S,2R)-3-[benzyl (cyanomethyl) amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1618	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-hydroxypropyl) amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1619	N <sup>1</sup> -[(1S,2R)-3-[(3-butoxypropyl) amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1620	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-([2-(2-hydroxyethyl) piperidin-1-yl] carbonyl)-5-methylbenzamide
1621	methyl N-[(2R,3S)-4-(3,5-difluorophenyl)-3-([3-[(dipropylamino) carbonyl]-5-methylbenzoyl] amino)-2-hydroxybutyl]-beta-alaninate
1622	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-(1-hydroxy-2-propylpentyl)benzamide
1623	N <sup>1</sup> -[(1S,2R)-3-(benzyl amino)-1-(3-chloro-5-fluorobenzyl)-2-hydroxypropyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1624	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-4-[(methylsulfonyl) amino]butanamide
1625	N <sup>1</sup> -[(1S,2R)-3-([3-(1-benzothien-2-yl) benzyl] amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1626	3-(benzyloxy)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)isoxazole-5-carboxamide
1627	2-[(benzyloxy) carbonyl] amino)-7-[(cyclopropylmethyl) amino]-1,2,4,5,7-pentadeoxy-5-(3,5-difluorobenzyl)-1-[(1-propylbutyl) sulfonyl]-D-threo-hept-3-ulose trifluoroacetate
1629	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-5-(1H-

	pyrazol-1-yl)pentanamide
1630	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(2-furymethyl)-5-oxopyrrolidine-3-carboxamide
1632	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(5-hydroxypentyl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1633	3-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1-methyl-1-phenylethyl)amino]propyl]amino)sulfonyl]-N,N-dipropylbenzamide
1634	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylpiperidine-1,3-dicarboxamide
1635	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N <sup>3</sup> ,N <sup>3</sup> -diethylpiperidine-1,3-dicarboxamide
1636	5-bromo-N <sup>1</sup> -((1S,2R)-2-hydroxy-1-(pentafluorobenzyl)-3-[(3-(trifluoromethyl)benzyl)amino]propyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1637	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(methylsulfonyl)amino]benzamide
1638	N-((1S,2R)-1-(3-bromobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-[(dipropylamino)sulfonyl]propanamide
1639	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(thien-2-ylmethyl)propyl]propanamide
1640	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethoxypropyl)amino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1641	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(thien-2-ylmethyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1642	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxy-4-(phenylsulfonyl)butanamide
1643	N <sup>1</sup> -[(1S,2R)-1-(3,5-dichlorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1645	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3,3-dimethylbutyl)amino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1646	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3-bromobenzyl)-2-hydroxypropyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1647	N <sup>1</sup> -[(1S,2R)-1-(3-chloro-5-fluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-

	N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1648	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(1,3-diphenylpropyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1649	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1S)-1-(hydroxymethyl)propyl]amino}propyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1650	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3S)-2-oxoazepan-3-yl]amino}propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1651	N <sup>1</sup> -cyclohexyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}pentanediamide
1652	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(3-methylbenzyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1653	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -[(2-propylpentyl)sulfonyl]-beta-alaninamide
1654	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(1,3-thiazol-2-yl)benzamide dihydrochloride
1656	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-[methyl(phenyl)amino]propyl)amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1657	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(4-methylbenzyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1658	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-oxo-1-(thien-2-ylmethyl)pyrrolidine-3-carboxamide
1659	4-[(butylthio)methyl]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-2-furamide
1660	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2-hydroxyethyl)amino]sulfonylbenzamide
1661	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methylcyclohexyl)amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1662	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2-oxo-1,3-oxazolidin-3-yl)benzamide
1663	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1H-pyrrol-1-yl)benzamide



1665	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1,3,4,5-tetrahydrothiopyrano[4,3-b]indole-8-carboxamide
1666	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N <sup>4</sup> -[2-(trifluoromethyl)phenyl]succinamide
1667	N <sup>1</sup> -[(1S,2R)-1-(3-bromobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1668	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4,5-dimethyl-2-(1H-pyrrol-1-yl)thiophene-3-carboxamide
1669	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,3-dihydroxypropyl)amino]-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1670	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2S)-2-hydroxypropyl]amino}propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1671	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-1-methylpropyl]amino}propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1672	2-chloro-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(methylsulfonyl)benzamide
1673	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-hydroxyethyl)amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1674	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-1-(3-methoxybenzyl)-3-[(3-methoxybenzyl)amino]propyl]propanamide
1675	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-{methyl[(trifluoromethyl)sulfonyl]amino}benzamide
1676	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-hydroxy-6-(1-hydroxy-2,2-dimethylpropyl)pyridine-2-carboxamide
1677	N <sup>1</sup> -[(1S,2R)-3-[(1,3-dicyclohexylpropyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1678	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2,2'-bithiophene-5-carboxamide
1679	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(1H-imidazol-1-yl)butanamide
1680	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

	ethylbenzyl) amino]-2-hydroxypropyl}-2,3-dihydroxy-N <sup>4</sup> -(4-methoxyphenyl) succinamide
1682	N <sup>1</sup> -{(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl) amino]-1-[3-(trifluoromethyl)benzyl]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1683	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(thien-2-ylmethyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1684	N <sup>1</sup> -[(1S,2R)-3-{[2-(aminocarbonyl)-1H-indol-6-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1685	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3-bromobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1686	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-2-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)butanamide
1687	3-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-4-(methylsulfonyl)thiophene-2-carboxamide
1688	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-ethylpropyl) amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1689	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-({[(5R)-3-ethyl-2-oxo-1,3-oxazolidin-5-yl]methyl}amino)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1690	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-5-methyl-7-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
1691	N <sup>1</sup> -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-N <sup>2</sup> -[(methylthio)acetyl]-3-[(1-propylbutyl) sulfonyl]alaninamide hydrochloride
1692	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,3-dimethylcyclohexyl) amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1693	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-4,5-dimethoxy-1-benzothiophene-2-carboxamide
1694	N <sup>1</sup> -[(1S,2R)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1695	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-({[(5S)-3-ethyl-2-oxo-1,3-oxazolidin-5-

	yl)methyl}amino)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1696	N <sup>1</sup> -{(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1697	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(3,5-dioxo-1,2,4-triazolidin-4-yl)benzamide
1698	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-hydroxy-3-[(3-methoxyphenyl)sulfonyl]propanamide hydrochloride
1699	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-methylcyclohexyl)amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1700	N <sup>1</sup> -[(1S,2R)-3-[(2-{4-[(3-chlorobenzyl)oxy]phenyl)ethyl}amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1701	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxy-4-oxo-4-thien-3-ylbutanamide
1702	N <sup>1</sup> -{(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1703	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxy-4-oxo-4-[3-(trifluoromethyl)phenyl]butanamide
1704	N <sup>1</sup> -{(1S,2R)-2-hydroxy-3-(isopentylamino)-1-[3-(trifluoromethoxy)benzyl]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1705	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[1-(hydroxymethyl)-3-(methylthio)propyl]amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1706	2-(1H-1,2,3-benzotriazol-1-yl)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}hexanamide
1707	N <sup>1</sup> -[(1S,2R)-1-(3-fluoro-4-methylbenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1708	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[[1-(propylbutyl)sulfonyl]methyl]propanamide
1709	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[[1-(trifluoromethyl)sulfonyl]amino]butanamide
1710	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

	ethylbenzyl) amino]-2-hydroxypropyl}-2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetamide
1712	N <sup>1</sup> -(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([1-(hydroxymethyl)propyl]amino)propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1713	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3,5-dichlorobenzyl)-2-hydroxypropyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1714	N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-[(2-hydroxyethyl)(propyl)amino]sulfonyl}propanamide hydrochloride
1715	5-(benzylthio)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]nicotinamide
1716	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1H-pyrazole-5-carboxamide
1717	6-chloro-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazole-5-carboxamide
1718	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1H-benzimidazole-2-carboxamide
1719	N <sup>1</sup> -[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1720	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-6-hydroxy-4,7-dimethoxy-1-benzofuran-5-carboxamide
1721	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(4-methylcyclohexyl)amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1722	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl][1,2,4]triazolo[4,3-a]pyridine-6-carboxamide
1723	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-hydroxy-4-oxo-4-thien-2-ylbutanamide
1724	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3,5-dichlorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1725	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(2-hydroxy-5-methylphenyl)-4-oxobutanamide
1726	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

	ethylbenzyl) amino]-2-hydroxypropyl}-3-phenoxybenzamide
1727	4-[(aminocarbonyl) amino]-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}benzamide
1728	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1S)-1-(hydroxymethyl)-3-(methylthio)propyl] amino}propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1729	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-7-hydroxy-4-oxochromane-2-carboxamide
1730	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1S)-1-(hydroxymethyl)-3-methylbutyl] amino}propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1731	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-1-(hydroxymethyl)propyl] amino}propyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1732	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1-methyl-3-phenylpropyl) amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1733	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-2-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazole-4-carboxamide
1734	N <sup>1</sup> -[(1S,2R)-1-[3-(benzyloxy)benzyl]-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1735	N-[(1S,2R)-1-(4-chlorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-3-[(dipropylamino) sulfonyl]propanamide
1736	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N <sup>3</sup> -pentylmalonamide
1737	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-(trifluoromethoxy)benzamide
1738	3-[(dipropylamino) sulfonyl]-N-[(1S,2R)-1-(3-fluoro-4-methylbenzyl)-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl]propanamide
1739	N-[(1S,2R)-1-(3-chloro-5-fluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino) sulfonyl]propanamide
1740	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[(1-propylbutyl) sulfonyl]methyl]propanamide
1741	N <sup>1</sup> -[4-(acetylamino)phenyl]-N <sup>4</sup> -[(1S,2R)-1-(3,5-

	difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)succinamide
1742	3-(1-cyanoethyl)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]benzamide
1743	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N <sup>4</sup> -(5-phenyl-1,3,4-thiadiazol-2-yl)succinamide
1744	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-[3-(trifluoromethoxy)benzyl]propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1745	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[2-(2-oxo-2-pyrrolidin-1-ylethoxy)phenyl]amino}propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1746	N <sup>1</sup> -[(1S,2R)-1-(4-chlorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1747	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-(1,1-dioxidotetrahydrothien-2-yl)acetamide
1748	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(4-chlorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1749	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-hex-1-ynylnicotinamide
1750	N-[(1S,2R)-1-(3-bromobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino)sulfonyl]propanamide
1751	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-methoxyisoxazole-5-carboxamide
1752	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2,3-dimethyl-1H-indole-7-carboxamide
1753	4-(3-chlorophenyl)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-hydroxy-4-oxobutanamide
1755	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-(1-methyl-1H-indol-3-yl)-2-oxoacetamide
1756	N <sup>1</sup> -[(1S,2R)-1-(3-fluoro-4-methylbenzyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1757	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(4-methylbenzyl)propyl]propanamide
1758	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3-fluoro-4-methylbenzyl)-2-hydroxypropyl]-N <sup>3</sup> ,N <sup>3</sup> -

	dipropylbenzene-1,3,5-tricarboxamide
1759	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-[5-(4-methylphenyl)-2H-tetrazol-2-yl]acetamide
1760	N-[(1S,2R)-1-(3,5-dichlorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-[(dipropylamino)sulfonyl]propanamide
1761	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(thien-2-ylmethyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1762	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-methyl-3-phenylisoxazole-4-carboxamide
1764	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N <sup>2</sup> -[(methylsulfonyl)acetyl]-N <sup>2</sup> -pentylglycinamide
1765	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(1H-indol-3-yl)-4-oxobutanamide
1766	N <sup>1</sup> -(5-benzyl-1,3,4-thiadiazol-2-yl)-N <sup>4</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]succinamide
1767	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(3-fluoro-4-methoxyphenyl)-4-oxobutanamide
1768	ethyl 4-[(2R,3S)-4-(3,5-difluorophenyl)-3-[(3-[(dipropylamino)carbonyl]-5-methylbenzoyl)amino]-2-hydroxybutyl]amino)piperidine-1-carboxylate
1769	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(2-fluorobenzoyl)-1H-pyrrole-2-carboxamide
1770	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(4-chlorobenzyl)-2-hydroxypropyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1772	N <sup>1</sup> -[(1S,2R)-2-hydroxy-1-(4-hydroxybenzyl)-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1773	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-(4-morpholin-4-ylphenyl)acetamide
1774	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-[3-(trifluoromethoxy)benzyl]propyl]propanamide
1775	N <sup>1</sup> -benzyl-N <sup>1</sup> -(1-cyclopropylethyl)-N <sup>4</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]succinamide
1776	N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-

	3-[(3-methoxybenzyl)amino]propyl}-3-(2,5-dimethylbenzoyl)-5-methylbenzamide
1777	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>4</sup> -(2-methoxy-5-methylphenyl)succinamide
1778	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(3-hydroxyphenyl)acetamide
1779	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[hydroxy(2-methylphenyl)methyl]-5-methylbenzamide
1780	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(ethylthio)nicotinamide
1781	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[4-(2-furoyl)piperazin-1-yl]-4-oxobutanamide
1782	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3-fluoro-4-methylbenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1783	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-oxoisindoline-1-carboxamide
1784	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(ethylthio)benzamide
1785	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}thieno[2,3-b]quinoline-2-carboxamide
1786	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(4-methyl-1,3-oxazol-2-yl)benzamide
1788	N-(2-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]phenyl)-N-methyl-2-furamide
1789	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxy-4-(3-methoxyphenyl)-4-oxobutanamide
1790	N <sup>1</sup> -[(1S,2R)-3-(cycloheptylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1791	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1792	1 3-[(dipropylamino)sulfonyl]-N-{(1S,2R)-1-(3-fluoro-5-hydroxybenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}propanamide



1793	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-(3-fluoro-5-hydroxybenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]propanamide hydrochloride
1794	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-hydroxy-1H-indole-2-carboxamide
1795	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2,2-dimethylchromane-8-carboxamide
1796	6-benzyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]pyrazine-2-carboxamide 4-oxide
1797	2-[[[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]amino]carbonyl]amino]-N,N-dipropylethanesulfonamide
1798	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1799	N-[(1S,2R)-3-(benzylamino)-1-(3-chloro-5-fluorobenzyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
1800	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(4-methoxyphenyl)-4-oxobutanamide
1802	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-methyl-4-oxo-3,4-dihydrophthalazine-1-carboxamide
1803	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3,4-dihydro-2H-1,5-benzodioxepine-7-carboxamide
1804	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-[4-(2,5-dioxopyrrolidin-1-yl)phenoxy]acetamide
1806	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide
1807	N <sup>1</sup> -[(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1808	N <sup>1</sup> -[(1S,2R)-1-(3-chloro-5-fluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
1809	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-6-fluoro-2-hydroxyquinoline-4-carboxamide
1810	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

	ethylbenzyl) amino]-2-hydroxypropyl}-4-oxo-4-thien-2-ylbutanamide
1811	N <sup>3</sup> -[({(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl} amino) carbonyl]-N <sup>1</sup> ,N <sup>1</sup> -dipropyl-beta-alaninamide
1812	N <sup>1</sup> -{(1R,2R)-2-hydroxy-3-[(3-methoxybenzyl) amino]-1-[(phenylthio)methyl]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1814	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R,2S)-1-(hydroxymethyl)-2-methylbutyl] amino}propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1815	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-2-(phenoxymethyl) benzamide
1816	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N <sup>5</sup> -(2,4-difluorophenyl) pentanediamide
1817	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N <sup>5</sup> -(4,6-dimethylpyrimidin-2-yl) pentanediamide
1818	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-3-(3-methoxybenzoyl)-5-methylbenzamide
1819	N <sup>1</sup> -{(1S,2R)-1-[3-(benzyloxy)benzyl]-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1820	4-(3,4-dichlorophenyl)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-4-oxobutanamide
1821	methyl 4-[(2R,3R)-2-[(3-[(dipropylamino) carbonyl]-5-methylbenzoyl) amino]-3-hydroxy-4-[(3-methoxybenzyl) amino]butyl] benzoate
1822	N <sup>1</sup> -(4-acetylphenyl)-N <sup>5</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl} pentanediamide
1824	N <sup>1</sup> -{(1R,2R)-2-hydroxy-3-[(3-methoxybenzyl) amino]-1-[(phenylthio)methyl]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1825	2-[(3-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl) amino]-3-oxopropyl]thio}-N-methylbenzamide
1826	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-3-[(1-propylbutyl) thio]propanamide
1827	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

	ethylbenzyl) amino]-2-hydroxypropyl}-N <sup>4</sup> -(4-ethoxyphenyl) succinamide
1828	N <sup>1</sup> -[(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1829	2-{{[(2R,3S)-4-(3,5-difluorophenyl)-3-({3-[(dipropylamino)carbonyl]-5-methylbenzoyl}amino)-2-hydroxybutyl]amino}ethyl 3-methoxyphenylcarbamate
1830	3-(benzyloxy)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]benzamide
1831	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{{[(1S)-2-hydroxy-1-methylethyl]amino}propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1832	N <sup>1</sup> -[(1S,2R)-2-hydroxy-1-(pentafluorobenzyl)-3-{{3-(trifluoromethyl)benzyl]amino}propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1833	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-4-(4-hydroxyphenyl)-4-oxobutanamide
1834	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl) amino]-1-[3-(trifluoromethyl)benzyl]propyl]propanamide
1835	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-3-(piperidin-3-ylsulfonyl)benzamide
1836	6-chloro-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-4-hydroxyquinoline-2-carboxamide
1837	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl) amino]-1-(thien-2-ylmethyl)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
1838	N <sup>1</sup> -[(1S)-1-[(1R)-1-hydroxy-2-[(3-methoxybenzyl) amino]ethyl]-3-methylbutyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1839	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-(6-oxo-3-phenylpyridazin-1(6H)-yl)acetamide
1840	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-3-{4-[(methylsulfonyl) amino]phenyl}propanamide
1842	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methylbenzyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1843	3-(2-chlorophenoxy)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl) amino]propyl]propanamide

1844	N <sup>1</sup> -[(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1845	Structure possibly contains peptides which are not supported in current version!
1846	1 N-[(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-[(dipropylamino)sulfonyl]propanamide hydrochloride
1847	N-[(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-[(dipropylamino)sulfonyl]propanamide hydrochloride
1848	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(4-methylphenyl)-4-oxobutanamide
1849	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N <sup>4</sup> -[3-(trifluoromethyl)phenyl]succinamide
1850	N <sup>1</sup> -[(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1851	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-(5-pyridin-2-yl-2H-tetraazol-2-yl)acetamide
1852	Structure possibly contains peptides which are not supported in current version!
1853	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(3-methylbenzyl)propyl]propanamide
1854	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]isoxazole-5-carboxamide
1855	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-(3,5-dimethoxyphenoxy)acetamide
1856	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(2,5-dimethyl-1H-pyrrol-1-yl)-3-hydroxybenzamide
1857	N <sup>1</sup> -[(1S,2R)-1-(3-bromobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
1858	N <sup>1</sup> -[5-(cyclopentylmethyl)-1,3,4-thiadiazol-2-yl]-N <sup>4</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]succinamide
1859	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-[3-(trifluoromethyl)benzyl]propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide

1860	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(3-oxo-1,2-benzisothiazol-2(3H)-yl)acetamide
1861	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[1-methyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrrol-3-yl]amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1862	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(3,4-difluorophenyl)-4-oxobutanamide
1863	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2-naphthyl)-4-oxobutanamide
1864	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4,6-diethoxypyridine-2-carboxamide
1865	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(5-methyl-1H-pyrrol-2-yl)-4-oxobutanamide
1866	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-([2-(methylamino)ethyl]amino)sulfonyl)benzamide dihydrochloride
1867	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-methyl-5-(4-methylbenzoyl)benzamide
1868	N <sup>1</sup> -[(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-3-(benzylamino)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1869	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(piperazin-1-ylsulfonyl)benzamide
1870	N <sup>1</sup> -[(1S,2R)-3-([2-[4-(aminosulfonyl)phenyl]ethyl]amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1871	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1872	N <sup>1</sup> -[(1S,2R)-1-(4-fluoro-3-methylbenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1873	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(3-oxo-2,1-benzisothiazol-1(3H)-yl)propanamide
1874	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2,6-dihydroxypyrimidin-4-yl)acetamide
1875	N <sup>1</sup> -((1S,2R)-2-hydroxy-3-[(3-

	methoxybenzyl) amino]-1-[3-(trifluoromethyl)benzyl]propyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
1876	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-hydroxybenzyl)propyl]-3-[(dipropylamino)sulfonyl]propanamide
1877	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(3,4-difluorophenyl)-2-methyl-4-oxobutanamide
1878	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N <sup>5</sup> -(2-pyridin-2-ylethyl)pentanediamide
1879	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-[2-(4-fluorophenyl)-1,3-benzoxazol-5-yl]acetamide
1880	N <sup>2</sup> -(anilinocarbonyl)-N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]glycinamide
1881	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-(1,3-dithian-2-yl)-3-furamide
1882	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-[2-oxo-2-(propylamino)ethyl]benzamide
1883	N-[(1S,2R)-3-(benzylamino)-1-(3-bromobenzyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
1884	N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]-3-(2-fluorophenyl)propanamide
1885	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-methylthiophene-2-carboxamide
1886	2-[4-(benzyloxy)phenyl]-N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]acetamide
1887	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-[(5,7-dimethyl[1,2,4]triazolo[4,3-a]pyrimidin-3-yl)thio]acetamide
1888	N <sup>1</sup> -(1-acetyl-2,3-dihydro-1H-indol-7-yl)-N <sup>4</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]succinamide
1889	N <sup>1</sup> -(3-acetylphenyl)-N <sup>5</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]pentanediamide
1890	3-(4-chlorophenoxy)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-hydroxypropanamide

1891	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxypropyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1892	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(3-methylbenzyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1893	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-7-carboxamide
1894	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methylbenzyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1895	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,2,3-thiadiazol-4-yl)benzamide
1896	N-{(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(dipropylamino)sulfonyl]propanamide
1897	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[[1-(propylbutyl)sulfonyl]methyl]propanamide
1898	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1899	N <sup>1</sup> -{(1S,2R)-3-(benzylamino)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1900	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[1-methyl-3-(methylthio)-1H-indol-2-yl]acetamide
1901	N <sup>1</sup> -[(1S,2R)-1-(3,5-dichlorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1902	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2-furyl)-4-oxobutanamide
1903	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)propanamide
1904	2-[2-(acetylamino)-1,3-thiazol-4-yl]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}acetamide
1905	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]-2-phenylacetamide
1906	N <sup>1</sup> -[(1S,2R)-1-(4-chlorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide

1907	4-(1,3-benzothiazol-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)butanamide
1908	N <sup>1</sup> -(3-chloro-4-fluorophenyl)-N <sup>4</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)succinamide
1909	N <sup>1</sup> -[(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1910	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(2-oxo-2,3-dihydroquinazolin-4-yl)thio]acetamide
1911	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-methyl-5-(2-methylbenzoyl)benzamide
1913	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methylbenzyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1914	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-propoxybenzamide
1915	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-methyl-1H-indole-2-carboxamide
1916	5-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(3-methyl-4H-1,2,4-triazol-4-yl)benzamide
1917	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(3,4-difluorophenyl)-2-methoxy-4-oxobutanamide
1918	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(3-thien-2-yl-1H-pyrazol-1-yl)acetamide
1919	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>5</sup> -phenylpentanediamide
1920	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-thioxo-1,3-benzothiazol-3(2H)-yl)acetamide
1923	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(3-hydroxy-4-methylphenyl)acetamide
1924	N <sup>1</sup> -[(1S,2R)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1925	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-7-fluoro-4H-imidazo[5,1-c][1,4]benzoxazine-3-



	carboxamide
1926	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-4-oxobutanamide
1927	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-benzofuran-3-carboxamide
1928	N <sup>1</sup> -(3,4-dichlorophenyl)-N <sup>3</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)malonamide
1929	N <sup>1</sup> -((1S,2R)-3-(benzylamino)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxypropyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1930	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-2-hydroxy-1-methylethyl]amino)propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1931	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(3-methylbenzyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1932	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>5</sup> -pyridin-3-ylpentanediamide
1933	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-4-oxo-4H-chromene-6-carboxamide
1934	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(1H-imidazol-1-yl)propyl]amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1935	3-[(dipropylamino)sulfonyl]-N-((1S,2R)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)propanamide
1936	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-1-(4-hydroxybenzyl)-3-(isopentylamino)propyl]propanamide
1937	N <sup>1</sup> -[(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1938	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(thien-2-ylmethyl)propyl]propanamide
1939	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(2,2-dimethylpropanoyl)amino]-2-hydroxybenzamide
1940	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methoxybenzyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1941	N-((1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl)-3-

	{[(3-methoxybenzyl)amino]sulfonyl}benzamide
1943	N-[6-({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)-6-oxohexyl]-2-furamide
1944	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-[(1-phenyl-4,5-dihydro-1H-tetrazol-5-yl)thio]acetamide
1945	4-acetyl-4-amino-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]cyclohexa-1,5-diene-1-sulfonamide
1946	N-[(1S,2S)-1-benzyl-2-hydroxy-3-[(3-(trifluoromethyl)benzyl)amino]propyl]-3-[(3-methoxybenzyl)amino]sulfonyl}benzamide
1947	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(3,4-dihydro-2H-chromen-6-yl)-4-oxobutanamide
1948	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methoxybenzyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1949	N <sup>1</sup> -[(1S,2R)-1-(3-fluoro-4-methylbenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
1950	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]indolizine-2-carboxamide
1951	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-[3-(trifluoromethoxy)benzyl]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1952	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]nicotinamide 1-oxide
1953	N-[(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino)sulfonyl]propanamide
1954	2-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]amino)-2-oxoethyl carbamate
1955	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2,3-dihydro-1H-cyclopenta[b]quinoline-9-carboxamide
1956	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-methyl-1H-pyrazole-5-carboxamide
1957	N-[5-({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)-5-oxopentyl]benzamide
1958	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

	ethylbenzyl) amino]-2-hydroxypropyl}-4-[(methoxymethyl)thio]benzamide
1959	3-(1,3-benzothiazol-2-yl)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-3-methoxypropanamide
1960	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-3-[[ (methylamino) carbonyl] amino]-3-thien-3-ylpropanamide
1961	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-5-pyridin-2-ylthiophene-2-carboxamide
1962	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxypropyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1963	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-(5,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyridin-3-yl)acetamide
1964	N <sup>1</sup> -[(1S,2R)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1965	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-isobutyl-1,3-dioxoisindoline-5-carboxamide
1967	5-(acetylamino)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-furamide
1968	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-N <sup>2</sup> -(4-methoxyphenyl)acetyl]glycinamide
1969	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]isoquinoline-4-carboxamide
1970	N <sup>1</sup> -[(1S,2R)-1-[3-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1971	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-(4-hydroxy-3-methoxyphenyl)acetamide
1972	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-[(4-phenyl-4H-1,2,4-triazol-3-yl)thio]acetamide
1973	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-(3,5-dimethoxyphenyl)acetamide
1974	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(3-methoxybenzyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
1975	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

	ethylbenzyl) amino]-2-hydroxypropyl}-2-(2-ethyl-4H-[1,2,4]triazolo[1,5-a]benzimidazol-4-yl) acetamide
1977	7-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-1-benzofuran-2-carboxamide
1978	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanamide
1979	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-(2-oxo-2H-1,3-benzoxazin-3(4H)-yl)propanamide
1980	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-2-(pyrimidin-2-ylthio)acetamide
1981	N <sup>1</sup> -[3-(aminocarbonyl)-4,5,6,7-tetrahydro-1-benzothien-2-yl]-N <sup>4</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)succinamide
1982	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]acetamide
1983	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)quinoline-6-carboxamide
1985	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-oxobutanamide
1986	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-(1H-indol-3-yl)-1H-pyrazole-5-carboxamide
1987	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-2-hydroxy-4-[[ (methylamino) carbonothioyl] amino]benzamide
1988	6-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)nicotinamide
1989	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-4-(3-hydroxyphenyl)-4-oxobutanamide
1990	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-2-(phthalazin-1-ylthio)acetamide
1991	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-2-[(1-oxidopyridin-2-yl)thio]acetamide
1992	3-(acetyl amino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-

	hydroxypropyl}-5-fluoro-1H-indole-2-carboxamide
1993	N-((1S,2S)-1-benzyl-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-3-{[(3-chlorobenzyl)amino]sulfonyl}benzamide
1995	N <sup>1</sup> -[(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-3-(benzylamino)-2-hydroxypropyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
1996	4-(3,4-dichlorophenyl)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxy-3-methyl-4-oxobutanamide
1997	3-[(dipropylamino)sulfonyl]-N-{(1S,2R)-2-hydroxy-3-(isopentylamino)-1-[3-(trifluoromethoxy)benzyl]propyl}propanamide
1998	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>4</sup> -(5-methyl-1,3,4-thiadiazol-2-yl)succinamide
1999	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2-ethyl-1H-benzimidazol-1-yl)acetamide
2000	N-{(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(dipropylamino)sulfonyl]propanamide
2001	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2-oxo-1,3-benzoxazol-3(2H)-yl)propanamide
2002	N-[(1S,2R)-1-(3,5-dichlorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2003	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>4</sup> -(6-methylpyridin-2-yl)succinamide
2004	ethyl (4R)-4-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]-1,3-oxazolidine-3-carboxylate
2005	N-{(1R,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-glycylbenzamide dihydrochloride
2006	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(1-methyl-1H-imidazol-2-yl)benzamide
2007	4-(acetylamino)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}butanamide trifluoroacetate
2008	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-D-leucinamide

2009	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(pyrrolidin-3-ylsulfonyl)benzamide
2010	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-[(dipropylamino)methyl]benzamide dihydrochloride
2011	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[ (1R)-1-(hydroxymethyl)-3-methylbutyl]amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2012	N <sup>1</sup> -[(1S,2R)-3-[tert-butyl(cyclohexyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2013	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[ (1S)-1-(hydroxymethyl)-2,2-dimethylpropyl]amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2014	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-([ (2R)-1-ethylpyrrolidin-2-yl]methyl)amino]-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2015	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[[3-(dimethylamino)-2,2-dimethylpropyl]amino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2016	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[[2-(diisopropylamino)ethyl]amino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2017	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[[ (1-ethylpyrrolidin-2-yl)methyl]amino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2018	N <sup>1</sup> -[(1S,2R)-3-[(1-benzylpyrrolidin-3-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2019	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-pyrrolidin-1-ylpropyl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2020	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[[3-(dimethylamino)propyl]amino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2021	N <sup>1</sup> -[(1S,2R)-3-[[2-(acetylamino)ethyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2022	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[2-(6-oxo-1,4,5,6-tetrahydropyridazin-3-

	yl)phenyl]amino}propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2023	N <sup>1</sup> -[(1S,2R)-3-[7-chloro-1-(2-hydroxy-3-methoxyphenyl)-3,4-dihydroisoquinolin-2(1H)-yl]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2024	N <sup>1</sup> -[(1S,2R)-3-{[4-(1-cyanocyclopentyl)phenyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2025	N <sup>1</sup> -[(1S,2R)-3-({4-[4-(acetylamino)phenoxy]phenyl}amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2026	N <sup>1</sup> -[(1S,2R)-3-[(4-benzoyl-2,3-dimethylphenyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2027	N <sup>1</sup> -[(1S,2R)-3-[(2-amino-2-oxo-1-phenylethyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2028	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{4-[(1-methyl-1H-imidazol-2-yl)methyl]piperazin-1-yl}propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2029	N <sup>1</sup> -[(1S,2R)-1-[3,5-bis(trifluoromethyl)benzyl]-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2030	(1S,2R)-N <sup>1</sup> -[2-(tert-butylthio)ethyl]-N <sup>2</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}cyclopropane-1,2-dicarboxamide
2031	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide
2032	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1-methyl-1H-benz[ <i>g</i> ]indazole-3-carboxamide
2033	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-methyl-1,3-thiazole-4-carboxamide
2034	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-methoxy-1H-pyrrole-3-carboxamide
2035	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-9-oxo-1,2,3,9-tetrahydrocyclopenta[ <i>b</i> ]chromene-7-carboxamide

2036	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)acetamide
2037	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)acetamide
2038	2-[2-(1,3-benzoxazol-2-yl)phenoxy]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide
2039	5-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-morpholin-4-ylbenzamide
2040	3-(3-chloroisoxazol-5-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)propanamide
2041	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(6-methoxy-1,1'-biphenyl-3-yl)-4-oxobutanamide
2042	4-(1-benzofuran-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-oxobutanamide
2043	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide
2044	2-(1-benzofuran-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methylpropanamide
2045	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-methoxy-1-benzofuran-2-carboxamide
2046	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[4-(1H-pyrrol-1-yl)phenyl]propanamide
2047	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1H-imidazo[1,2-b]pyrazole-6-carboxamide
2048	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(4-methyl-1,3-thiazol-2-yl)thio]acetamide
2049	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methoxy-4-(methylthio)benzamide
2050	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxy-4-(propionylamino)benzamide
2051	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-[[4-methylphenyl)sulfonyl]amino]-4-oxohexanamide
2052	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1H-



	benzimidazole-5-carboxamide
2053	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-2-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)propanamide
2054	7-(acetylamino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methylquinoline-5-carboxamide
2054A	N <sup>3</sup> -(tert-butoxycarbonyl)-N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-b-alaninamide
2055	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-hydroxy-3-propylhexanamide
2056	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-phenyl-2-(1H-pyrrol-1-yl)acetamide
2057	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-methyl-5-phenyl-1H-pyrazole-3-carboxamide
2058	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(3-oxo-2,3-dihydro-1H-isoindol-1-yl)acetamide
2059	4-[2-(acetylamino)-4,5-dimethylphenyl]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-oxobutanamide
2060	6-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)pyrazine-2-carboxamide 4-oxide
2061	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-methoxypyrazine-2-carboxamide 4-oxide
2062	2-(1H,1'H-2,2'-biimidazol-1-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide
2063	5-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,3-dihydro-1-benzofuran-7-carboxamide
2064	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-([1,2,4]triazolo[4,3-b]pyridazin-6-ylthio)acetamide
2065	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methyl-1-pyridin-4-yl-1H-1,2,3-triazole-4-carboxamide
2066	2-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-

	oxo-3,4-dihydroquinazoline-6-carboxamide
2067	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(7-methoxy-1-benzofuran-2-yl)-4-oxobutanamide
2068	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(2-ethyl-1-oxo-2,3-dihydro-1H-indol-5-yl)oxy]propanamide
2069	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)pyrazine-2-carboxamide 4-oxide
2070	7-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)quinoline-2-carboxamide
2071	2-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(3,4-dimethoxyphenyl)-2-methylpropanamide
2072	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxy-5-(propionylamino)benzamide
2073	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[2-oxo-5-(trifluoromethyl)pyridin-1(2H)-yl]propanamide
2074	5-(4-chlorophenyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-furamide
2075	4-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(1H-pyrrol-1-yl)thiophene-2-carboxamide
2076	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3,5-bis(methylthio)isothiazole-4-carboxamide
2077	2-chloro-4-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide
2078	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(methoxyacetyl)amino]-3-phenylpropanamide
2079	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-fluoro-4-morpholin-4-ylbenzamide
2080	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(1-oxidithiomorpholin-4-yl)butanamide
2081	4-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
2082	N-{2-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

	ethylbenzyl) amino]-2-hydroxypropyl) amino) carbonyl] phenyl)-5-methyl-2-furamide
2083	1-(cyanomethyl)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-1H-pyrrole-2-carboxamide
2084	N <sup>1</sup> -(2-chloropyridin-3-yl)-N <sup>4</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]succinamide
2085	3-(cyclopentyloxy)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-4-methoxybenzamide
2086	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-(5-pyrrolidin-1-yl-2H-tetraazol-2-yl)acetamide
2087	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxamide
2088	1-(4-acetylphenyl)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]piperidine-4-carboxamide
2089	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-methyl-2-(1H-1,2,4-triazol-1-yl)propanamide
2090	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-5-(piperidin-1-ylmethyl)-2-furamide
2091	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-methyl-2,3-dihydro-1-benzothiophene-2-carboxamide 1,1-dioxide
2092	2-(2,1,3-benzoxadiazol-5-yl)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-1,3-thiazole-4-carboxamide
2093	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-4,5-dihydrofuro[2,3-g][2,1]benzisoxazole-8-carboxamide
2094	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-[(4-methyl-1,2,3-thiadiazol-5-yl)thio]acetamide
2095	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-1-(2-furoyl)-4-hydroxyprolinamide
2096	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide
2097	4,5-dichloro-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-

	hydroxypropyl}isothiazole-3-carboxamide
2098	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>5</sup> -(1,3-thiazol-2-yl)pentanediamide
2099	N-acetyl-4-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}phenylalaninamide
2100	8-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-hydroxycinnoline-3-carboxamide
2101	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,6-dioxohexahydropyrimidine-4-carboxamide
2102	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(5-methyl-4-phenyl-1,3-oxazol-2-yl)benzamide
2103	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenylimidazo[1,2-a]pyridine-6-carboxamide
2104	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]propanamide
2105	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3-thiazole-4-carboxamide
2106	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-2-phenyl-2H-1,2,3-triazole-4-carboxamide
2107	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)butanamide
2108	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-dimethyl-1H-thieno[2,3-c]pyrazole-5-carboxamide
2109	4-(1,3-benzodioxol-5-yl)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}butanamide
2110	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)isoxazole-4-carboxamide
2111	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-(dimethylamino)-1-methylethyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2112	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(2-methylmorpholin-4-yl)propyl]-5-methyl-

	N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2113	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{2-[hydroxy(phenyl)methyl]-4-methylpiperazin-1-yl}propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2114	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2R)-2-methylbutyl]amino)propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2115	N <sup>1</sup> -[(1S,2R)-3-{[4-(diethylamino)-1-methylbutyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2116	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-hydroxy-1,1-dimethylethyl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2117	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(2-methylpiperidin-1-yl)propyl]amino}propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2118	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]amino}propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2119	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methyl-4,5,6,7-tetrahydro-3H-3λ4-[1,3]thiazolo[5,4-c]pyridin-2-yl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2120	N <sup>1</sup> -[(1S,2R)-3-[(3-ethylbenzyl)amino]-2-hydroxy-1-(1H-pyrazol-1-ylmethyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2121	3,5-bis(acetylamino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide
2122	N <sup>1</sup> -[4-(aminosulfonyl)phenyl]-N <sup>4</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)succinamide
2123	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[methyl(methylsulfonyl)amino]benzamide
2124	1-acetyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)piperidine-4-carboxamide
2125	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(4-methoxyphenoxy)propanamide
2126	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>4</sup> -

	methylsuccinamide
2127	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>4</sup> -(2,6-dimethylphenyl)succinamide
2128	N-acetyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-phenylalaninamide
2129	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(4-methylphenyl)sulfonyl]acetamide
2130	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[[ (ethylamino) carbonyl] amino] benzamide
2131	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-phenyl-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxamide
2132	4-(cyclopentyloxy)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide
2133	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>4</sup> -pyridin-3-ylsuccinamide
2134	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>4</sup> -phenylsuccinamide
2135	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydroxybenzamide
2136	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1H-1,2,4-triazol-1-yl)pentanamide
2137	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenyl-1,3-oxazole-4-carboxamide
2138	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-7-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxamide
2139	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-{4-[(methylsulfonyl)amino]phenyl}-4-oxobutanamide
2140	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-hydroxy-7-methoxy-1-benzofuran-5-carboxamide
2141	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-hydroxy-7-methoxy-1-benzothiophene-5-carboxamide

2142	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-2-carboxamide
2143	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5,6-dihydro-4H-cyclopenta[b]thiophene-2-carboxamide
2144	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-thiazole-4-carboxamide
2145	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2-pyridin-2-yl-1,3-thiazol-4-yl)acetamide
2146	N <sup>1</sup> -[5-(aminosulfonyl)-1,3,4-thiadiazol-2-yl]-N <sup>4</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}succinamide
2147	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxy-6-neopentylpyridine-2-carboxamide
2148	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(4-fluorophenyl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxamide
2149	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepine-3-carboxamide
2150	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-3-furamide
2151	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-furamide
2152	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2-hydroxyethoxy)benzamide
2153	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}thiophene-2-carboxamide
2154	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> ,N <sup>2</sup> -dimethylphthalamide
2155	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-2-phenyl-1,3-oxazole-4-carboxamide
2156	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-

	hydroxybutanamide
2157	2-(2H-1,2,3-benzotriazol-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)butanamide
2158	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1H-indazole-3-carboxamide
2159	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-hydroxyquinoxaline-2-carboxamide
2160	2-(acetyl amino)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4,5-dimethylthiophene-3-carboxamide
2161	N <sup>1</sup> -(2-cyanophenyl)-N <sup>4</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)succinamide
2162	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-ethyl-1H-indole-2-carboxamide
2163	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-benzofuran-2-carboxamide
2164	1-benzyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3,5-dimethyl-1H-pyrazole-4-carboxamide
2165	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>2</sup> -(4-methylphenyl)sulfonyl]glycinamide
2166	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4,8-dihydroxyquinoline-2-carboxamide
2167	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(1,1-dioxidotetrahydrothien-3-yl)acetamide
2168	methyl 5-(((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]-1H-benzimidazol-2-ylcarbamate
2169	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-methyl-1,3-benzoxazol-5-yl)acetamide
2170	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[ethyl(methyl)amino]-4-hydroxypyrimidine-5-carboxamide
2171	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-pyridin-4-yl-1,3-benzoxazol-5-yl)acetamide
2172	4-[2-(diethylamino)ethoxy]-N-((1S,2R)-1-(3,5-



	difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide
2173	3-(aminosulfonyl)-4-chloro-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide
2174	2-(diethylamino)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-hydroxypyrimidine-5-carboxamide
2175	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5,6,7,8-tetrahydro-4H-cyclohepta[c]isoxazole-3-carboxamide
2176	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N <sup>4</sup> ,N <sup>4</sup> -diphenylsuccinamide
2177	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-6-hydroxy-4-methylpyridine-2-carboxamide
2178	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-phenylimidazo[1,2-a]pyridine-7-carboxamide
2179	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}quinoline-4-carboxamide
2180	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)acetamide
2181	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-methoxy-1H-indole-2-carboxamide
2182	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(3,5-dimethyl-1H-pyrazol-1-yl)benzamide
2183	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-methylisoxazole-3-carboxamide
2184	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-methylisoxazole-5-carboxamide
2185	2-(1-benzothien-4-yl)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}acetamide
2186	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxamide
2187	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1-

	benzothiophene-2-carboxamide
2188	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-hydroxynicotinamide
2189	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>3</sup> -[(4-methylphenyl)sulfonyl]-beta-alaninamide
2190	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxyquinoline-4-carboxamide
2191	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(5-phenyl-1H-tetraazol-1-yl)acetamide
2192	4-[(cyclobutylcarbonyl)amino]methyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamide
2193	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2-oxo-1,3-benzoxazol-3(2H)-yl)butanamide
2194	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(1,3-dioxooctahydro-2H-isoindol-2-yl)butanamide
2195	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>2</sup> -(tetrahydrofuran-2-ylmethyl)phthalamide
2196	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2,3-dihydro-1H-indol-1-yl)-4-oxobutanamide
2197	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)thieno[3,2-b]pyridine-6-carboxamide
2198	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(6-methoxy-1H-benzimidazol-2-yl)thio]acetamide
2199	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)thieno[2,3-c]pyridine-2-carboxamide
2200	2-(1H-benzimidazol-2-ylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)propanamide
2201	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(2,4-difluorobenzyl)oxy]propanamide
2202	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5,6-dimethyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-carboxamide

2203	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(2-fluorophenyl)-5-oxopyrrolidine-3-carboxamide
2204	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(5-methyl-1H-tetraazol-1-yl)benzamide
2205	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)thiophene-3-carboxamide
2206	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-(trifluoromethoxy)-1H-indole-2-carboxamide
2207	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-phenyl-5-propyl-1H-pyrazole-4-carboxamide
2208	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[(pyridin-2-ylthio)methyl]-2-furamide
2209	5-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-morpholin-4-ylpyrimidine-4-carboxamide
2210	5-chloro-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-methyl-1-phenyl-1H-pyrazole-4-carboxamide
2211	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide
2212	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,1,3-benzoxadiazole-5-carboxamide
2213	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(imidazo[1,2-a]pyridin-2-ylmethyl)thio]acetamide
2214	2-(acetylamino)-N-((1R,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-1,3-oxazole-4-carboxamide
2215	N-((1S,2R)-1-[3-(cyclohexylmethyl)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)acetamide
2216	1 2-[[[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino]carbonyl]amino]-N,N-dipropylethanesulfonamide hydrochloride
2217	2-(3-azabicyclo[3.2.2]non-3-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)acetamide
2218	2-(4-benzoylphenoxy)-N-((1S,2R)-1-(3,5-

	difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}propanamide
2219	N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]-4-(7-methoxy-2,3-dihydro-1-benzofuran-4-yl)-4-oxobutanamide
2220	N-[(1S,2R)-1-[3-(cyclohexylmethyl)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-[[trifluoromethyl)sulfonyl]amino]benzamide hydrochloride
2221	N <sup>1</sup> -[(1S,2R)-1-[3-(cyclohexylmethyl)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide hydrochloride
2222	3-chloro-N-[(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl]benzamide
2223	3-chloro-N-[(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]benzamide
2224	3-chloro-N-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl]benzamide
2225	3-chloro-N-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]benzamide
2226	N-[(1S,2S)-1-benzyl-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl]-3-chlorobenzamide
2227	N-[(1S,2S)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-chlorobenzamide
2228	3-[[3-(3-chlorobenzyl)amino]sulfonyl]-N-[(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl]benzamide
2229	3-[[3-(3-chlorobenzyl)amino]sulfonyl]-N-[(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]benzamide
2230	3-[[3-(3-chlorobenzyl)amino]sulfonyl]-N-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl]benzamide
2231	3-[[3-(3-chlorobenzyl)amino]sulfonyl]-N-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]benzamide
2232	N-[(1S,2S)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-[[3-

	chlorobenzyl) amino] sulfonyl} benzamide
2233	N-[(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl) amino] propyl]-3-[(3-methoxybenzyl) amino] sulfonyl} benzamide
2234	N-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[[3-(trifluoromethyl) benzyl] amino] propyl]-3-[[3-(methoxybenzyl) amino] sulfonyl} benzamide
2235	N-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[(3-methoxybenzyl) amino] propyl]-3-[(3-methoxybenzyl) amino] sulfonyl} benzamide
2236	N-[(1S,2S)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino] propyl]-3-[(3-methoxybenzyl) amino] sulfonyl} benzamide
2237	N <sup>1</sup> -[(1R,2S)-2-hydroxy-3-[(3-methoxybenzyl) amino]-1-(4-methylbenzyl) propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2238	N <sup>1</sup> -[(1R,2S)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl) propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2239	N <sup>1</sup> -[(1R,2S)-2-hydroxy-3-[(3-methoxybenzyl) amino]-1-(4-methylbenzyl) propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2240	N <sup>1</sup> -[(1R,2S)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl) propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2241	N <sup>1</sup> -[(1R,2S)-2-hydroxy-3-[(3-methoxybenzyl) amino]-1-(4-methylbenzyl) propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2242	N <sup>1</sup> -[(1R,2S)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl) propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2243	3-[(dipropylamino) sulfonyl]-N-[(1R,2S)-2-hydroxy-3-[(3-methoxybenzyl) amino]-1-(4-methylbenzyl) propyl] propanamide
2244	3-[(dipropylamino) sulfonyl]-N-[(1R,2S)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl) propyl] propanamide
2245	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl) amino]-1-(4-methylbenzyl) propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2246	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methylbenzyl) propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2247	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl) propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide

2248	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methylbenzyl)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2249	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]propanamide
2250	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(4,5-dimethyl-2-furoyl)-5-methylbenzamide
2251	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-hydroxy-3-(isopentylsulfonyl)propanamide hydrochloride
2252	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(2-methoxyethyl)(propyl)amino]sulfonylpropanamide hydrochloride
2253	N <sup>1</sup> -{(1R,2R)-3-(benzylamino)-2-hydroxy-1-[(phenylthio)methyl]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2254	N <sup>1</sup> -{(1R,2R)-2-hydroxy-3-(isopentylamino)-1-[(phenylthio)methyl]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2255	N <sup>1</sup> -{(1S,2R)-3-(benzylamino)-1-[4-(benzyloxy)benzyl]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2256	N <sup>1</sup> -[(1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2257	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(1-naphthylmethyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2259	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(1-naphthylmethyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2260	N <sup>1</sup> -[(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2261	N <sup>1</sup> -{(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)benzyl]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2262	N <sup>1</sup> -[(1S,2R)-2-hydroxy-1-(4-hydroxybenzyl)-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2263	N <sup>1</sup> -{(1S)-1-[(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl]but-3-ynyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2264	N <sup>1</sup> -{(1S)-1-[(1R)-2-(benzylamino)-1-hydroxyethyl]but-3-ynyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide

2265	N <sup>1</sup> -{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]but-3-ynyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2266	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(cyclohexylmethyl)-2-hydroxypropyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2267	N <sup>1</sup> -[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2268	N <sup>1</sup> -{(1S)-1-[(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl]-3-methylbutyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2270	N <sup>1</sup> -{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]-3-methylbutyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2271	N <sup>1</sup> -{(1R,2R)-3-(benzylamino)-2-hydroxy-1-[(phenylthio)methyl]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2272	N <sup>1</sup> -{(1R,2R)-2-hydroxy-3-(isopentylamino)-1-[(phenylthio)methyl]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2273	N <sup>1</sup> -{(1S,2R)-3-(benzylamino)-1-[4-(benzyloxy)benzyl]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2274	N <sup>1</sup> -[(1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2275	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(1-naphthylmethyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2277	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(1-naphthylmethyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2278	N <sup>1</sup> -[(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2279	N <sup>1</sup> -{(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)benzyl]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2280	N <sup>1</sup> -[(1S,2R)-1-[3-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2281	N <sup>1</sup> -[(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2282	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(thien-2-ylmethyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2283	N <sup>1</sup> -{(1S)-1-[(1R)-1-hydroxy-2-[(3-

	methoxybenzyl) amino] ethyl] but-3-ynyl)-5-methyl-N <sup>3</sup> , N <sup>3</sup> -dipropylisophthalamide
2284	N <sup>1</sup> -{(1S)-1-[(1R)-2-(benzylamino)-1-hydroxyethyl]but-3-ynyl}-5-methyl-N <sup>3</sup> , N <sup>3</sup> -dipropylisophthalamide
2285	N <sup>1</sup> -{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]but-3-ynyl}-5-methyl-N <sup>3</sup> , N <sup>3</sup> -dipropylisophthalamide
2286	N <sup>1</sup> -[(1S, 2R)-1-(cyclohexylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> , N <sup>3</sup> -dipropylisophthalamide
2288	N <sup>1</sup> -{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]-3-methylbutyl}-5-methyl-N <sup>3</sup> , N <sup>3</sup> -dipropylisophthalamide
2289	N <sup>1</sup> -{(1R, 2R)-2-hydroxy-3-[(3-methoxybenzyl) amino]-1-[(phenylthio)methyl]propyl}-N <sup>5</sup> , N <sup>5</sup> -dipropylpentanediamide
2290	N <sup>1</sup> -{(1R, 2R)-3-(benzylamino)-2-hydroxy-1-[(phenylthio)methyl]propyl}-N <sup>5</sup> , N <sup>5</sup> -dipropylpentanediamide
2291	N <sup>1</sup> -{(1R, 2R)-2-hydroxy-3-(isopentylamino)-1-[(phenylthio)methyl]propyl}-N <sup>5</sup> , N <sup>5</sup> -dipropylpentanediamide
2292	N <sup>1</sup> -{(1S, 2R)-3-(benzylamino)-1-[4-(benzyloxy)benzyl]-2-hydroxypropyl}-N <sup>5</sup> , N <sup>5</sup> -dipropylpentanediamide
2293	N <sup>1</sup> -[(1S, 2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> , N <sup>5</sup> -dipropylpentanediamide
2295	N <sup>1</sup> -[(1S, 2R)-3-(benzylamino)-2-hydroxy-1-(1-naphthylmethyl)propyl]-N <sup>5</sup> , N <sup>5</sup> -dipropylpentanediamide
2296	N <sup>1</sup> -[(1S, 2R)-2-hydroxy-3-(isopentylamino)-1-(1-naphthylmethyl)propyl]-N <sup>5</sup> , N <sup>5</sup> -dipropylpentanediamide
2298	N <sup>1</sup> -[(1S, 2R)-3-(benzylamino)-1-(2-furylmethyl)-2-hydroxypropyl]-N <sup>5</sup> , N <sup>5</sup> -dipropylpentanediamide
2299	N <sup>1</sup> -[(1S, 2R)-1-(2-furylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> , N <sup>5</sup> -dipropylpentanediamide
2300	N <sup>1</sup> -{(1S, 2R)-1-[3-(benzyloxy)benzyl]-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-N <sup>5</sup> , N <sup>5</sup> -dipropylpentanediamide
2301	N <sup>1</sup> -{(1S, 2R)-3-(benzylamino)-1-[3-(benzyloxy)benzyl]-2-hydroxypropyl}-N <sup>5</sup> , N <sup>5</sup> -dipropylpentanediamide
2302	N <sup>1</sup> -[(1S, 2R)-1-[3-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> , N <sup>5</sup> -dipropylpentanediamide



2304	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(4-fluorobenzyl)-2-hydroxypropyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2305	N <sup>1</sup> -[(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2306	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(thien-2-ylmethyl)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2307	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(thien-2-ylmethyl)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2308	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-hydroxybenzyl)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2309	N <sup>1</sup> -[(1S,2R)-2-hydroxy-1-(4-hydroxybenzyl)-3-(isopentylamino)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2310	N <sup>1</sup> -{(1S)-1-[(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl]but-3-ynyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2311	N <sup>1</sup> -{(1S)-1-[(1R)-2-(benzylamino)-1-hydroxyethyl]but-3-ynyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2312	N <sup>1</sup> -{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]but-3-ynyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2313	N <sup>1</sup> -{(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2314	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(cyclohexylmethyl)-2-hydroxypropyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2315	N <sup>1</sup> -[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2316	N <sup>1</sup> -{(1S)-1-[(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl]-3-methylbutyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2317	N <sup>1</sup> -{(1S)-1-[(1R)-2-(benzylamino)-1-hydroxyethyl]-3-methylbutyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2318	N <sup>1</sup> -{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]-3-methylbutyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2319	3-[(dipropylamino)sulfonyl]-N-{(1R,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-[(phenylthio)methyl]propyl}propanamide
2320	N-{(1R,2R)-3-(benzylamino)-2-hydroxy-1-[(phenylthio)methyl]propyl}-3-

	[(dipropylamino) sulfonyl]propanamide
2321	3-[(dipropylamino) sulfonyl]-N-[(1R,2R)-2-hydroxy-3-(isopentylamino)-1-[(phenylthio)methyl]propyl]propanamide
2322	N-[(1S,2R)-3-(benzylamino)-1-[4-(benzyloxy)benzyl]-2-hydroxypropyl]-3-[(dipropylamino) sulfonyl]propanamide
2323	N-[(1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino) sulfonyl]propanamide
2324	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(1-naphthylmethyl)propyl]-3-[(dipropylamino) sulfonyl]propanamide
2325	3-[(dipropylamino) sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(1-naphthylmethyl)propyl]propanamide
2326	N-[(1S,2R)-3-(benzylamino)-1-(2-furylmethyl)-2-hydroxypropyl]-3-[(dipropylamino) sulfonyl]propanamide
2327	3-[(dipropylamino) sulfonyl]-N-[(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-(isopentylamino)propyl]propanamide
2328	N-[(1S,2R)-1-[3-(benzyloxy)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-[(dipropylamino) sulfonyl]propanamide
2329	N-[(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)benzyl]-2-hydroxypropyl]-3-[(dipropylamino) sulfonyl]propanamide
2330	N-[(1S,2R)-1-[3-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino) sulfonyl]propanamide
2331	N-[(1S,2R)-3-(benzylamino)-1-(4-fluorobenzyl)-2-hydroxypropyl]-3-[(dipropylamino) sulfonyl]propanamide
2332	3-[(dipropylamino) sulfonyl]-N-[(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]propanamide
2333	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(thien-2-ylmethyl)propyl]-3-[(dipropylamino) sulfonyl]propanamide
2334	3-[(dipropylamino) sulfonyl]-N-[(1S)-1-[(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl]but-3-ynyl]propanamide
2335	N'-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-[(1Z)-prop-1-en-1-yl]benzyl)amino]propyl]-5-methyl-N,N-dipropylisophthalamide
2335	N-[(1S)-1-[(1R)-2-(benzylamino)-1-hydroxyethyl]but-3-ynyl]-3-

	[(dipropylamino)sulfonyl]propanamide
2336	3-[(dipropylamino)sulfonyl]-N-[(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]but-3-ynyl]propanamide
2337	N-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-[(dipropylamino)sulfonyl]propanamide
2338	N-[(1S,2R)-3-(benzylamino)-1-(cyclohexylmethyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2339	methyl [3-([(2R,3S)-4-(3,5-difluorophenyl)-3-[(3-[(dipropylamino)carbonyl]-5-methylbenzoyl]amino)-2-hydroxybutyl]amino)methyl]phenyl]methylcarbamate
2339	N-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2340	3-[(dipropylamino)sulfonyl]-N-[(1S)-1-[(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl]-3-methylbutyl]propanamide
2341	N-[(1S)-1-[(1R)-2-(benzylamino)-1-hydroxyethyl]-3-methylbutyl]-3-[(dipropylamino)sulfonyl]propanamide
2342	3-[(dipropylamino)sulfonyl]-N-[(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]-3-methylbutyl]propanamide
2343	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(3-methoxybenzyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2346	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-isopropylbenzyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2348	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methoxybenzyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2349	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methoxybenzyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2350	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(4-fluoro-3-methylbenzyl)-2-hydroxypropyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2351	N <sup>1</sup> -[(1S,2R)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2352	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-isopropylbenzyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2353	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-isopropylbenzyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -

	dipropylisophthalamide
2354	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-[3-(trifluoromethoxy)benzyl]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2355	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methoxybenzyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2356	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methoxybenzyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2357	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(4-fluoro-3-methylbenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2358	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[4R)-2,2-dioxido-3,4-dihydro-1H-2,1-benzothiazin-4-yl]amino]-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide
2359	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[4S)-2,2-dioxido-3,4-dihydro-1H-2,1-benzothiazin-4-yl]amino]-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide
2358	N <sup>1</sup> -[(1S,2R)-1-(4-fluoro-3-methylbenzyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2359	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-[3-(trifluoromethyl)benzyl]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2360	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methylbenzyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2361	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2362	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2363	N <sup>1</sup> -[(1S,2R)-2-hydroxy-1-(3-methoxybenzyl)-3-[(3-methoxybenzyl)amino]propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2364	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(3-methoxybenzyl)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2365	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methoxybenzyl)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2366	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3-chloro-5-fluorobenzyl)-2-hydroxypropyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2367	N <sup>1</sup> -[(1S,2R)-1-(3-chloro-5-fluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> ,N <sup>5</sup> -

	dipropylpentanediamide
2368	N <sup>1</sup> -{(1S,2R)-1-(3,5-dichlorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2369	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3,5-dichlorobenzyl)-2-hydroxypropyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2370	N <sup>1</sup> -[(1S,2R)-1-(3,5-dichlorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2371	N <sup>1</sup> -{(1S,2R)-2-hydroxy-1-(4-isopropylbenzyl)-3-[(3-methoxybenzyl)amino]propyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2311	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-isopropylbenzyl)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2312	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-isopropylbenzyl)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2313	N <sup>1</sup> -{(1S,2R)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2314	N <sup>1</sup> -{(1S,2R)-3-(benzylamino)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxypropyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2315	N <sup>1</sup> -[(1S,2R)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2316	N <sup>1</sup> -{(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-[3-(trifluoromethoxy)benzyl]propyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2317	N <sup>1</sup> -{(1S,2R)-3-(benzylamino)-2-hydroxy-1-[3-(trifluoromethoxy)benzyl]propyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2318	N <sup>1</sup> -{(1S,2R)-2-hydroxy-3-(isopentylamino)-1-[3-(trifluoromethoxy)benzyl]propyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2319	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3-fluoro-4-methylbenzyl)-2-hydroxypropyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2320	N <sup>1</sup> -[(1S,2R)-1-(3-fluoro-4-methylbenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2321	N <sup>1</sup> -{(1S,2R)-2-hydroxy-1-(4-methoxybenzyl)-3-[(3-methoxybenzyl)amino]propyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2322	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-

	methoxybenzyl)propyl]-N <sup>5</sup> ,N <sup>5</sup> - dipropylpentanediamide
2323	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methoxybenzyl)propyl]-N <sup>5</sup> ,N <sup>5</sup> - dipropylpentanediamide
2324	N <sup>1</sup> -{(1S,2R)-1-(4-chlorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>5</sup> ,N <sup>5</sup> - dipropylpentanediamide
2325	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(4-chlorobenzyl)-2-hydroxypropyl]-N <sup>5</sup> ,N <sup>5</sup> - dipropylpentanediamide
2326	N <sup>1</sup> -[(1S,2R)-1-(4-chlorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> ,N <sup>5</sup> - dipropylpentanediamide
2327	N <sup>1</sup> -{(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}- N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2328	N <sup>1</sup> -[(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-3-(benzylamino)-2-hydroxypropyl]-N <sup>5</sup> ,N <sup>5</sup> - dipropylpentanediamide
2329	N <sup>1</sup> -[(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> ,N <sup>5</sup> - dipropylpentanediamide
2330	N <sup>1</sup> -{(1S,2R)-1-(4-fluoro-3-methylbenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}- N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2331	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(4-fluoro-3-methylbenzyl)-2-hydroxypropyl]-N <sup>5</sup> ,N <sup>5</sup> - dipropylpentanediamide
2332	N <sup>1</sup> -[(1S,2R)-1-(4-fluoro-3-methylbenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> ,N <sup>5</sup> - dipropylpentanediamide
2333	N <sup>1</sup> -{(1S,2R)-3-(benzylamino)-2-hydroxy-1-[3-(trifluoromethyl)benzyl]propyl}-N <sup>5</sup> ,N <sup>5</sup> - dipropylpentanediamide
2335	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(3-methylbenzyl)propyl]-N <sup>5</sup> ,N <sup>5</sup> - dipropylpentanediamide
2336	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(3-methylbenzyl)propyl]-N <sup>5</sup> ,N <sup>5</sup> - dipropylpentanediamide
2337	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methylbenzyl)propyl]-N <sup>5</sup> ,N <sup>5</sup> - dipropylpentanediamide
2338	N <sup>1</sup> -{(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}- N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2339	N <sup>1</sup> -{(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxypropyl}-N <sup>5</sup> ,N <sup>5</sup> -

	dipropylpentanediamide
2340	N <sup>1</sup> -[(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2341	N <sup>1</sup> -[(1S,2R)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2342	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxypropyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2343	N <sup>1</sup> -[(1S,2R)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2344	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(3-bromobenzyl)-2-hydroxypropyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2345	N <sup>1</sup> -[(1S,2R)-1-(3-bromobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2346	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(3-methoxybenzyl)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2347	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methoxybenzyl)propyl]propanamide
2348	N-[(1S,2R)-3-(benzylamino)-1-(3,5-dichlorobenzyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2349	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-1-(4-isopropylbenzyl)-3-[(3-methoxybenzyl)amino]propyl]propanamide
2350	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-isopropylbenzyl)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2351	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-isopropylbenzyl)propyl]propanamide
2352	N-[(1S,2R)-3-(benzylamino)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2353	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxy-3-(isopentylamino)propyl]propanamide
2354	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-[3-(trifluoromethoxy)benzyl]propyl]-3-[(dipropylamino)sulfonyl]propanamide
2355	N-[(1S,2R)-3-(benzylamino)-1-(3-fluoro-4-methylbenzyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2356	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-(3-fluoro-4-methylbenzyl)-2-hydroxy-3-

	(isopentylamino)propyl}propanamide
2357	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-1-(4-methoxybenzyl)-3-[(3-methoxybenzyl)amino]propyl}propanamide
2358	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methoxybenzyl)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2359	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methoxybenzyl)propyl}propanamide
2360	N-[(1S,2R)-3-(benzylamino)-1-(4-chlorobenzyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2314	N-[(1S,2R)-1-(4-chlorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2315	N-[(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-3-(benzylamino)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2316	N-[(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2317	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-(4-fluoro-3-methylbenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}propanamide
2318	N-[(1S,2R)-3-(benzylamino)-1-(4-fluoro-3-methylbenzyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2319	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-(4-fluoro-3-methylbenzyl)-2-hydroxy-3-(isopentylamino)propyl}propanamide
2320	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-[3-(trifluoromethyl)benzyl]propyl]-3-[(dipropylamino)sulfonyl]propanamide
2321	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-[3-(trifluoromethyl)benzyl]propyl}propanamide
2322	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(3-methylbenzyl)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2323	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methylbenzyl)propyl}propanamide
2324	N-[(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2325	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}propanamide
2326	N-[(1S,2R)-3-(benzylamino)-1-(3-fluoro-4-



	methoxybenzyl)-2-hydroxypropyl]-3- [(dipropylamino)sulfonyl]propanamide
2327	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxy-3-(isopentylamino)propyl]propanamide
2328	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenyl-2-(4H-1,2,4-triazol-3-ylthio)acetamide
2329	1-acetyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenylprolinamide

A compound of the formula:

Compound #	Compound Structure
2330	

5

The compounds in the table immediately below were prepared essentially using the methods described above and illustrated below in the schemes.

10 The following compounds were named using the Advanced Chemistry Development Inc. (ACD) nomenclature program, IUPAC Name Batch Version 4.5. The website for ACD is [www.acdlabs.com](http://www.acdlabs.com).

2332	N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[ (3R,4S)-3-(hydroxymethyl)-6-isopropyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl]amino]propyl)-5-methyl-N,N-dipropylisophthalamide
2333	N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[ (3R,4S)-6-isopropyl-3-methyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl]amino]propyl)-5-methyl-N,N-dipropylisophthalamide
2334	N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[ (3R,4S)-6-isopropyl-2,2-dioxido-3-propyl-3,4-dihydro-1H-isothiochromen-4-yl]amino]propyl)-5-methyl-N,N-dipropylisophthalamide

2336	<i>N'</i> - ((1 <i>S</i> , 2 <i>R</i> ) - 1 - (3, 5-difluorobenzyl) - 2-hydroxy-3- {[(3 <i>S</i> , 4 <i>R</i> ) - 3 - (hydroxymethyl) - 6-isopropyl-2, 2- dioxido-3, 4-dihydro-1 <i>H</i> -isothiochromen-4- yl]amino}propyl) - 5-methyl- <i>N</i> , <i>N</i> - dipropylisophthalamide
2337	<i>N'</i> - ((1 <i>S</i> , 2 <i>R</i> ) - 1 - (3, 5-difluorobenzyl) - 2-hydroxy-3- {[(3 <i>S</i> , 4 <i>R</i> ) - 3 - (2-hydroxyethyl) - 6-isopropyl-2, 2- dioxido-3, 4-dihydro-1 <i>H</i> -isothiochromen-4- yl]amino}propyl) - 5-methyl- <i>N</i> , <i>N</i> - dipropylisophthalamide
2339	<i>N'</i> - ((1 <i>S</i> , 2 <i>R</i> ) - 1 - (3, 5-difluorobenzyl) - 2-hydroxy-3- {[(3 <i>S</i> , 4 <i>S</i> ) - 6-isopropyl-2, 2-dioxido-3-propyl-3, 4- dihydro-1 <i>H</i> -isothiochromen-4-yl]amino}propyl) - 5- methyl- <i>N</i> , <i>N</i> -dipropylisophthalamide
2340	<i>N'</i> - ((1 <i>S</i> , 2 <i>R</i> ) - 1 - (3, 5-difluorobenzyl) - 2-hydroxy-3- {[(3 <i>S</i> , 4 <i>S</i> ) - 6-isopropyl-3-methyl-2, 2-dioxido-3, 4- dihydro-1 <i>H</i> -isothiochromen-4-yl]amino}propyl) - 5- methyl- <i>N</i> , <i>N</i> -dipropylisophthalamide
2341	<i>N'</i> - ((1 <i>S</i> , 2 <i>R</i> ) - 1 - (3, 5-difluorobenzyl) - 2-hydroxy-3- {[(4 <i>R</i> ) - 6-isopropyl-2, 2-dioxido-3, 4-dihydro-1 <i>H</i> - isothiochromen-4-yl]amino}propyl) - 5-methyl- <i>N</i> , <i>N</i> - dipropylisophthalamide

The compounds in the table immediately below were prepared essentially using the methods described above and illustrated below in the schemes.

- 5 The following compounds were named using the Advanced Chemistry Development Inc. (ACD) nomenclature program, IUPAC Name Batch Version 4.5. The website for ACD is [www.acdlabs.com](http://www.acdlabs.com).

2342	<i>N</i> - { (1 <i>S</i> , 2 <i>R</i> ) - 1 - (3, 5-difluorobenzyl) - 3 - [(3-ethylbenzyl)amino] - 2-hydroxypropyl } - 3 - [(3-methoxypropyl) (methylsulfonyl)amino]benzamide
2343	<i>N</i> - { (1 <i>S</i> , 2 <i>R</i> ) - 1 - (3, 5-difluorobenzyl) - 3 - [(3-ethylbenzyl)amino] - 2-hydroxypropyl } - 4 - [(3-methoxypropyl) (methylsulfonyl)amino]benzamide
2344	<i>N</i> - { (1 <i>S</i> , 2 <i>R</i> ) - 1 - (3, 5-difluorobenzyl) - 3 - [(3-ethylbenzyl)amino] - 2-hydroxypropyl } - 4 - [(2-methoxyethyl) (methylsulfonyl)amino]benzamide
2345	<i>N</i> - { (1 <i>S</i> , 2 <i>R</i> ) - 1 - (3, 5-difluorobenzyl) - 3 - [(3-ethylbenzyl)amino] - 2-hydroxypropyl } - 6 - [(2-methoxyethyl) (methylsulfonyl)amino]nicotinamide
2346	<i>N</i> - { (1 <i>S</i> , 2 <i>R</i> ) - 1 - (3, 5-difluorobenzyl) - 3 - [(3-ethylbenzyl)amino] - 2-hydroxypropyl } - 6 - [(3-hydroxypropyl) (methylsulfonyl)amino]nicotinamide

2347	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-[(2-hydroxyethyl)(methylsulfonyl)amino]nicotinamide
2348	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-[(2-methoxyethyl)(methylsulfonyl)amino]nicotinamide
2349	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(2-methoxyethyl)(methylsulfonyl)amino]isonicotinamide
2350	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[(2-methoxyethyl)(methylsulfonyl)amino]nicotinamide
2351	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(3-hydroxypropyl)(methylsulfonyl)amino]isonicotinamide
2352	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(2-hydroxyethyl)(methylsulfonyl)amino]isonicotinamide
2353	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[(2-hydroxyethyl)(methylsulfonyl)amino]nicotinamide
2354	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[(3-hydroxypropyl)(methylsulfonyl)amino]nicotinamide
2355	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(3-methoxypropyl)(methylsulfonyl)amino]isonicotinamide
2356	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[(3-methoxypropyl)(methylsulfonyl)amino]nicotinamide
2357	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(methylsulfonyl)-1H-indole-5-carboxamide
2358	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(methylsulfonyl)indoline-5-carboxamide
2359	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(methylsulfonyl)indoline-4-carboxamide
2360	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(methylsulfonyl)indoline-6-carboxamide
2361	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-

	(methylsulfonyl)-1H-indole-4-carboxamide
2362	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[1-methyl-1-(methylsulfonyl)ethyl]benzamide
2363	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[1-methyl-1-(methylsulfonyl)ethyl]benzamide
2364	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(ethylsulfonyl)benzamide
2365	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(propylsulfonyl)benzamide
2366	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(pentylsulfonyl)benzamide
2367	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(2-hydroxyethyl)sulfonyl]benzamide
2368	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(2-methoxyethyl)sulfonyl]benzamide
2369	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(2-ethoxyethyl)sulfonyl]benzamide
2370	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(3-hydroxypropyl)sulfonyl]benzamide
2371	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,3-dihydro-1-benzothiophene-5-carboxamide; 1,1-dioxide
2372	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-benzothiophene-5-carboxamide; 1,1-dioxide
2374	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,3-dihydro-1-benzothiophene-6-carboxamide; 1,1-dioxide
2375	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-benzothiophene-6-carboxamide; 1,1-dioxide
2376	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-2,3-dihydro-1,2-benzisothiazole-6-carboxamide; 1,1-dioxide
2377	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-2,3-dihydro-1,2-benzisothiazole-5-carboxamide; 1,1-dioxide

2378	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-methyl-1,3-dihydro-2,1-benzisothiazole-6-carboxamide; 2,2-dioxide
2343	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-methyl-1,3-dihydro-2,1-benzisothiazole-5-carboxamide; 2,2-dioxide
2344	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,2-dimethylchromane-6-carboxamide
2345	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,2-dimethylchromane-7-carboxamide

The compounds in the table immediately below were prepared essentially using the methods described above and  
5 illustrated below in the schemes.

The following compounds were named using the Advanced Chemistry Development Inc. (ACD) nomenclature program, IUPAC Name Batch Version 4.5. The website for ACD is [www.acdlabs.com](http://www.acdlabs.com).

	Compound Name(s)
2346	benzyl (3R)-4-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino)-2,2,3-trimethyl-4-oxobutanoate
2347	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-4-(phenylsulfonyl)butanamide
2348	(3S)-tetrahydrofuran-3-yl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2349	N <sup>1</sup> -((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N <sup>3</sup> -(phenylsulfonyl)-beta-alaninamide
2350	N <sup>1</sup> -((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N <sup>3</sup> -(4-methylphenyl)sulfonyl]-beta-alaninamide
2351	N <sup>1</sup> -((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N <sup>3</sup> -(4-fluorophenyl)sulfonyl]-beta-alaninamide
2352	N <sup>1</sup> -((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N <sup>3</sup> -(4-methoxyphenyl)sulfonyl]-beta-alaninamide

2353	N <sup>1</sup> -{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>2</sup> -[(4-methylphenyl)sulfonyl]glycinamide
2354	N <sup>1</sup> -{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>2</sup> -[(4-fluorophenyl)sulfonyl]glycinamide
2355	N <sup>1</sup> -{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>2</sup> -[(4-methoxyphenyl)sulfonyl]glycinamide
2356	N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(4-chlorophenyl)sulfonyl]propanamide
2357	N <sup>1</sup> -{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>2</sup> -(benzylsulfonyl)glycinamide
2358	N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(4-fluorophenyl)sulfonyl]propanamide
2359	N <sup>1</sup> -{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>3</sup> -[(4-chlorophenyl)sulfonyl]-beta-alaninamide
2360	N <sup>1</sup> -{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>3</sup> -(benzylsulfonyl)-beta-alaninamide
2361	N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(4-methoxyphenyl)sulfonyl]propanamide
2362	N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(4-methylphenyl)sulfonyl]propanamide
2363	N <sup>1</sup> -benzyl-N <sup>4</sup> -{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2,2-dimethylsuccinamide
2364	N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)propanamide
2365	N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanamide
2366	(2R)-N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-methyl-3-(phenylsulfonyl)propanamide
2367	(2S)-N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-methyl-3-(phenylsulfonyl)propanamide
2368	N <sup>1</sup> -benzyl-N <sup>5</sup> -{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}pentanediamide
2369	N-{(1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-[(phenylsulfonyl)methyl]acrylamide

2370	N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-2-[(isopentylsulfonyl)methyl]acrylamide
2371	N <sup>1</sup> -[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-N <sup>3</sup> -[(dipropylamino)carbonyl]-beta-alaninamide
2372	N <sup>1</sup> -[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-N <sup>2</sup> -[(dipropylamino)carbonyl]glycinamide
2373	benzyl (4R)-4-[[[(1S,2R)-1-benzyl-3-[[3-(dimethylamino)-2,2-dimethylpropyl]amino]-2-hydroxypropyl]amino]carbonyl]-1,3-oxazolidine-3-carboxylate compound with methyl hydroperoxide (1:2)
2374	tert-butyl (2R,3S)-2-hydroxy-3-[(2-hydroxy-3-[(3-methoxyphenyl)sulfonyl]propanoyl)amino]-4-phenylbutyl (3-methoxybenzyl) carbamate
2383	N <sup>1</sup> -[(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2386	N <sup>1</sup> -[(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2405	N <sup>1</sup> -[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2406	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(cyclohexylmethyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2411	N <sup>1</sup> -[(1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2413	N <sup>1</sup> -[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2414	N <sup>1</sup> -[(1S,2R)-3-(benzylamino)-1-(cyclohexylmethyl)-2-hydroxypropyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2419	N <sup>1</sup> -[(1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2421	N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-[hydroxy(2-methylphenyl)methyl]-5-methylbenzamide
2426	N <sup>1</sup> -[(1R,2S)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2427	N <sup>1</sup> -[(1R,2S)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(4-methylbenzyl)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide

2428	N <sup>1</sup> -[(1R,2S)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2429	N <sup>1</sup> -[(1R,2S)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(4-methylbenzyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide
2440	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxy-4-(phenylsulfonyl)butanamide
2442	benzyl (2R,3S)-4-(3,5-difluorophenyl)-3-[(3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[[1-(propylbutyl)sulfonyl]methyl]propanoyl)amino]-2-hydroxybutyl (3-ethylbenzyl)carbamate
2445	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-7-(1H-imidazol-1-yl)-5,6-dihydronaphthalene-2-carboxamide
2446	2-[[[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino]carbonyl]amino}-N,N-dipropylethanesulfonamide hydrochloride
2447	benzyl (2R,3S)-4-(3,5-difluorophenyl)-2-hydroxy-3-({N-(3-phenylpropanoyl)-3-[(1-propylbutyl)sulfonyl]alanyl)amino)butyl (3-ethylbenzyl)carbamate
2448	N <sup>1</sup> -[(1S,2R)-3-[(benzyloxy)carbonyl](3-ethylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-N <sup>2</sup> -{(3S)-tetrahydrofuran-3-yloxy}carbonyl}-D-leucinamide
2449	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-([1,3]oxazolo[4,5-b]pyridin-2-ylthio)acetamide
2450	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(imidazo[1,2-a]pyridin-2-ylmethyl)thio]acetamide
2451	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(5,7-dimethyl[1,2,4]triazolo[4,3-a]pyrimidin-3-yl)thio]acetamide
2452	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,3-dihydro-1H-cyclopenta[b]quinoline-9-carboxamide
2453	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxamide
2454	1817 or N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-dioxoisindoline-5-carboxamide



2455	1-benzyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1H-imidazole-2-carboxamide
2456	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)thiophene-3-carboxamide
2457	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-isobutyl-1,3-dioxoisindoline-5-carboxamide
2458	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-oxo-2-phenylpyrazolidine-3-carboxamide
2459	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5,6-dimethyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-carboxamide
2460	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(2,4-difluorobenzyl)oxy]propanamide
2461	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]thieno[2,3-c]pyridine-2-carboxamide
2463	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(2-methyl-1H-benzimidazol-1-yl)-4-oxobutanamide
2464	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-(2,5-dioxopyrrolidin-1-yl)-4-methylbenzamide
2465	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]thieno[3,2-b]pyridine-6-carboxamide
2466	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(2,3-dihydro-1H-indol-1-yl)-4-oxobutanamide
2468	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-(1,3-dioxooctahydro-2H-isoindol-2-yl)butanamide
2469	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N <sup>3</sup> -(4-methylphenyl)sulfonyl-beta-alaninamide
2470	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-4-(1H-indol-3-yl)-4-oxobutanamide
2471	N <sup>2</sup> -(anilinocarbonothioyl)-N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]glycinamide
2472	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxamide

2473	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5,6,7,8-tetrahydro-4H-cyclohepta[c]isoxazole-3-carboxamide
2475	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>2</sup> -[(4-methylphenyl)sulfonyl]glycinamide
2477	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(3,5-dioxo-1,2,4-triazolidin-4-yl)benzamide
2478	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2-hydroxyethoxy)benzamide
2479	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(1,3-dithian-2-yl)-3-furamide
2481	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepine-3-carboxamide
2482	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(4-fluorophenyl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxamide
2484	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5,6-dihydro-4H-cyclopenta[b]thiophene-2-carboxamide
2485	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-2-carboxamide
2486	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-7-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxamide
2487	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-carboxamide
2488	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide
2489	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide
2490	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-7-fluoro-4H-imidazo[5,1-c][1,4]benzoxazine-3-carboxamide
2491	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(3-fluoro-4-methoxyphenyl)-4-oxobutanamide

2492	methyl 4-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)-4-oxobutyl-(dithiocarbamate)
2493	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)[1,2,4]triazolo[4,3-a]pyridine-6-carboxamide
2494	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-phenyl-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxamide
2495	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(4-methylphenyl)sulfonyl]acetamide
2496	3-(2-chlorophenyl)-2-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)propanamide
2498	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(4-methylphenyl)-4-oxobutanamide
2499	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2-hydroxy-5-methylphenyl)-4-oxobutanamide
2500	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzamide
2501	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-oxo-4-thien-2-ylbutanamide or 2379
2502	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-hydroxybenzamide
2503	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2,5-dioxopyrrolidin-1-yl)benzamide
2507	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[(trifluoroacetyl)amino]butanamide
2510	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(1-hydroxycyclopentyl)thio]acetamide
2511	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(2-oxocyclohexyl)propanamide
2512	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2-naphthyl)-4-oxobutanamide

2513	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-oxo-2,3-dihydro-1H-indazole-4-carboxamide
2514	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1,3-dimethyl-1H-thieno[2,3-c]pyrazole-5-carboxamide
2515	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>2</sup> -[(dimethylamino)sulfonyl]valinamide
2516	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2-furyl)-4-oxobutanamide
2517	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(5-methyl-4-phenyl-1,3-oxazol-2-yl)benzamide
2518	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2,6-dioxohexahydropyrimidine-4-carboxamide
2519	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5,7-dimethoxy-1-oxoindane-2-carboxamide
2521	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>5</sup> -(2-pyridin-2-ylethyl)pentanediamide
2522	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[4-(2-furoyl)piperazin-1-yl]-4-oxobutanamide
2523	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide
2524	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-oxo-1-(thien-2-ylmethyl)pyrrolidine-3-carboxamide
2525	2-[(cyanomethyl)thio]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)nicotinamide
2526	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-(2-furoyl)-4-hydroxyprolinamide
2527	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4,5-dihydrofuro[2,3-g][2,1]benzisoxazole-8-carboxamide
2528	methyl 3-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]-5-methylthiophene-2-sulfenate
2529	2-(acetylamino)-2-(1H-1,2,3-benzotriazol-1-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide

2530	1-[[ (cyclohexylamino) carbonyl] amino]-N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]cyclopropanecarboxamide
2531	N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-(2-ethyl-4H-[1, 2, 4] triazolo[1, 5-a]benzimidazol-4-yl)acetamide
2532	(2E)-N <sup>1</sup> -[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-N <sup>4</sup> -[4-(1, 3-oxazol-5-yl)phenyl]but-2-enediamide
2533	N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-1, 3, 4, 5-tetrahydrothiopyrano[4, 3-b]indole-8-carboxamide
2535	N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-4-(3, 4-dihydro-2H-1, 5-benzodioxepin-7-yl)-4-oxobutanamide
2536	N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-4-(1-oxidothiomorpholin-4-yl)butanamide
2537	N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-4-oxo-4-(2-thioxo-1, 3-benzothiazol-3(2H)-yl)butanamide
2538	N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-8H-thieno[2, 3-b]indole-2-carboxamide
2539	N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-3, 4-dihydro-2H-1, 5-benzodioxepine-7-carboxamide
2540	N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-4H-chromeno[3, 4-d]isoxazole-4-carboxamide
2542	N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-4-(3, 4-difluorophenyl)-4-oxobutanamide
2543	N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-4-(3, 4-difluorophenyl)-2-methyl-4-oxobutanamide
2544	N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-4-(3, 4-difluorophenyl)-2-methoxy-4-oxobutanamide
2545	N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-hydroxy-4-oxo-4-[3-(trifluoromethyl)phenyl]butanamide
2546	N-[(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-2-hydroxy-4-oxo-4-thien-2-ylbutanamide

2548	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(2-ethyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]propanamide
2549	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-oxoisindoline-1-carboxamide
2550	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(7-methoxy-1-benzofuran-2-yl)-4-oxobutanamide
2551	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4H-chromeno[3,4-d]isoxazole-8-carboxamide
2552	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-4-oxo-4H-chromene-6-carboxamide
2553	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-([1,2,4]triazolo[4,3-b]pyridazin-6-ylthio)acetamide
2554	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(1,1-dioxidotetrahydrothien-2-yl)acetamide
2555	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(3,4-dihydro-2H-chromen-6-yl)-4-oxobutanamide
2556	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-ethyl-3-oxoisindoline-1-carboxamide
2558	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(4-hydroxyphenyl)-4-oxobutanamide
2559	2-[(6-chloro[1,2,4]triazolo[4,3-b]pyridazin-3-yl)oxy]-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)acetamide
2560	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxy-4-(3-methoxyphenyl)-4-oxobutanamide
2561	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxy-4-oxo-4-thien-3-ylbutanamide
2562	3-chlorophenyl 4-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)-4-oxobutanoate
2563	4-(4-chloro-2-hydroxyphenyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-oxobutanamide
2565	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-6-[(4-methylphenyl)sulfonyl]amino)-4-oxohexanamide

2566	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(6-hydroxy-3-oxo-2,3-dihydroimidazo[2,1-b][1,3]thiazol-2-yl)acetamide
2567	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(4,5-dihydro-1,3-thiazol-2-ylthio)acetamide
2568	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1H-imidazo[1,2-b]pyrazole-6-carboxamide
2570	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(6-methoxy-1,1'-biphenyl-3-yl)-4-oxobutanamide
2571	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(4-methoxyphenyl)-4-oxobutanamide
2572	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-oxobutanamide
2573	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)acetamide
2574	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)acetamide
2575	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-9-oxo-1,2,3,9-tetrahydrocyclopenta[b]chromene-7-carboxamide
2576	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-methyl-1H-benzo[g]indazole-3-carboxamide
2577	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide
2578	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-(tetraazolo[1,5-b]pyridazin-6-ylthio)acetamide
2580	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(5-methyl-1H-pyrrol-2-yl)-4-oxobutanamide
2581	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-[[ (trifluoromethyl)sulfonyl]amino]butanamide
2582	N-[(1S,2R)-3-(2-acetyl-1-ethylhydrazino)-1-benzyl-2-hydroxypropyl]-2-[(methylsulfonyl)amino]-1,3-thiazole-4-carboxamide

2583	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-(1-hydroxy-2-propylpentyl)benzamide
2587	N <sup>1</sup> -[(1S,2R)-3-[(2-{4-[(3-chlorobenzyl)oxy]phenyl}ethyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2589	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-morpholin-4-ylpropyl)amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2597	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N <sup>2</sup> -[(methylsulfonyl)acetyl]-N <sup>2</sup> -pentylglycinamide
2598	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonylpropanamide
2599	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonylpropanamide
2600	ethyl 4-[(2R,3S)-3-[(3-[(dipropylamino)carbonyl]benzoyl)amino]-2-hydroxy-4-phenylbutyl]amino}piperidine-1-carboxylate
2601	N <sup>1</sup> -[(1S,2R)-1-benzyl-3-[(3R)-1-benzylpyrrolidin-3-yl]amino]-2-hydroxypropyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2602	methyl (2E)-2-[2-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]amino]-2-oxoethyl]-4-methylpent-2-enoate
2603	N <sup>1</sup> -[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-N <sup>4</sup> -(4-methoxybenzyl)succinamide
2604	N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-3-[(4-fluorophenyl)sulfonyl]amino}-3-methylbutanamide
2605	N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-9,10-dioxo-9,10-dihydroanthracene-2-carboxamide
2606	N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-4-(benzyloxy)benzamide
2607	N'-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-N-methyl-N-phenylurea
2608	N'-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-N,N-diisopropylurea
2609	N'-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-N,N-diphenylurea



2610	N'-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N,N-dimethylurea
2611	methyl 2-[[[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino]carbonyl]amino]benzoate
2613	2-methoxyethyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2612	phenyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2614	2-(benzyloxy)ethyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2615	prop-2-ynyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2616	(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2617	pentyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2618	neopentyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2621	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[4-oxo-4H-chromen-3-yl)methyl]amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2622	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)amino]propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2623	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide
2625	N <sup>1</sup> -[(1S,2R)-3-[(1-acetylpiperidin-3-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2627	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>3</sup> -ethoxy-5-methylisophthalamide
2628	N <sup>1</sup> -(allyloxy)-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methylisophthalamide
2629	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>3</sup> -isobutoxy-5-methylisophthalamide
2630	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-methyl-N <sup>3</sup> -(2,2,3,3,3-pentafluoropropyl)isophthalamide
2631	ethyl 4-[(3-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino]carbonyl]-5-methylbenzoyl)amino]butanoate

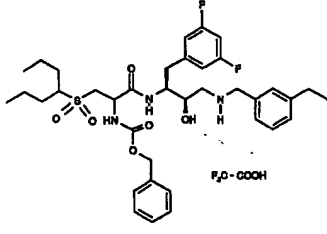
2632	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -bis(2,2,2-trifluoroethyl)isophthalamide
2633	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -ethyl-N <sup>3</sup> -[(1-ethylpiperidin-4-yl)carbonyl]-5-methylisophthalamide
2634	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -(2,2,3,3,4,4,4-heptafluorobutyl)-5-methylisophthalamide
2635	N <sup>1</sup> -(1-benzylpyrrolidin-3-yl)-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>1</sup> -ethyl-5-methylisophthalamide
2636	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> -(tetrahydrofuran-2-ylmethyl)isophthalamide
2638	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[ (3R)-2-oxoazepan-3-yl]amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2639	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazin-4-yl)amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2640	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[2-(4-methylpentanoyl)hydrazino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2641	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(3-ethylphenyl)sulfonyl]propanamide
2642	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,2,3,3,4,4-hexafluoro-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide
2643	N <sup>5</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenyl-N <sup>1</sup> ,N <sup>1</sup> -dipropylpentanediamide
2644	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(3-hydroxypropyl)(methylsulfonyl)amino]benzamide
2645	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(2-hydroxyethyl)(methylsulfonyl)amino]benzamide
2646	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[[ (2R)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide
2647	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(3-hydroxypropyl)(methylsulfonyl)amino]benzamide

The compounds in the table immediately below were prepared essentially using the methods described above and illustrated below in the schemes.

- 5 The following compounds were named using the Advanced Chemistry Development Inc. (ACD) nomenclature program, IUPAC Name Batch Version 4.5. The website for ACD is [www.acdlabs.com](http://www.acdlabs.com).

	Compound Name(s)	mass spec
2648	5-bromo-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
2649	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[[trifluoromethyl)sulfonyl]amino]benzamide	586.1
2657	N <sup>1</sup> -{(1S,2R)-1-(3,5-dichlorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide	643.2
2664	N <sup>1</sup> -[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(thien-2-ylmethyl)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide	581.3
2665	N <sup>1</sup> -{(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbenzene-1,3,5-tricarboxamide	593.3
2666	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(4-methyl-1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	647
2667	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropyl-5-(1,3-thiazol-2-yl)isophthalamide	649
2668	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(methylsulfonyl)amino]benzamide	532.2
2671	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	633
2672	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide hydrochloride	633.4
2675	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]propanamide hydrochloride	553

2677	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	635
2678	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-2-[(methylsulfonyl)amino]-1,3-thiazole-4-carboxamide	637.6
2679	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropyl-5-[[trifluoromethyl)sulfonyl]amino]isophthalamide	665
2680	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(isopentylsulfonyl)propanamide	525
2681	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[[1-methyl-1H-imidazol-4-yl)sulfonyl]amino}benzamide trihydrochloride	598.1
2682	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[[trifluoromethyl)sulfonyl]amino}benzamide	586
2684	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[[2-hydroxyethyl)(propyl)amino]sulfonyl]propanamide	556
2685	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(1,3-oxazol-2-yl)benzamide hydrochloride	506
2686	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[[2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	717
2687	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[[2-hydroxy-1,1-dimethylethyl)amino]sulfonyl]benzamide	590
2688	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[[3-hydroxypropyl)amino]sulfonyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	703
2689	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(methylsulfonyl)amino]-1,3-thiazole-4-carboxamide	539.1

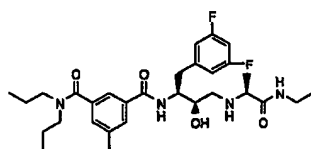
2690	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -(phenylacetyl)-3-[(1-propylbutyl)sulfonyl]alaninamide	686
2691	 racemic	702
2692	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(3-methylisoxazol-4-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide hydrochloride	647
2693	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-([2-(methylamino)ethyl]amino)sulfonyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide hydrochloride	702
2694	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[[2-(2-hydroxyethyl)amino]sulfonyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	689
2695	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(methylsulfonyl)amino]butanamide	499
2696	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(piperazin-1-ylsulfonyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	714
2697	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[methyl(methylsulfonyl)amino]benzamide	546
2698	5-[[bis(2-hydroxyethyl)amino]sulfonyl]-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	733
2699	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,8-dimethylquinoline-3-carboxamide	518. 3
2702	2-[[[(2R,3S)-4-(3,5-difluorophenyl)-3-[(3-(dipropylamino)carbonyl]-5-methylbenzoyl)amino]-2-hydroxybutyl]amino]ethyl 2,4-difluorophenylcarbamate	661. 7
2704	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropyl-5-(1H-pyrazol-4-yl)isophthalamide	632

2706	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-hydroxyisoxazole-5-carboxamide	446. 2
2707	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-(1-methyl-1H-imidazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	646
2708	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[ (2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl]-5-methylbenzamide hydrochloride	594. 3
2709	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[[ (2-hydroxyethyl)amino]sulfonyl]-N <sup>3</sup> -propylisophthalamide	647
2710	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-([ (1S)-2-hydroxy-1-methylethyl]amino)sulfonyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	703
2711	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N <sup>3</sup> ,N <sup>3</sup> -diethyl-5-(1,3-oxazol-2-yl)isophthalamide	605. 4
2712	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[[ (2S)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl]-5-methylbenzamide hydrochloride	594. 3
2713	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[[ (2S)-2-(hydroxymethyl)pyrrolidin-1-yl]sulfonyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	729
2714	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-([ (1R)-2-hydroxy-1-methylethyl]amino)sulfonyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	703
2716	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(2-ethyl-1-hydroxybutyl)benzamide	539. 3
2717	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-[(dimethylamino)sulfonyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	673. 1
2719	N <sup>1</sup> -[ (1S,2R)-3-[[2-(aminosulfonyl)ethyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	569. 6

2723	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(4-phenylbutyl)amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	594.5
2729	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -ethyl-N <sup>3</sup> -methyl-5-(1,3-oxazol-2-yl)isophthalamide	591.4
2730	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -methyl-5-(1,3-oxazol-2-yl)-N <sup>3</sup> -propylisophthalamide	605.4
2731	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropyl-5-(pyrrolidin-1-ylsulfonyl)isophthalamide hydrochloride	699.1
2732	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-5-[[2-hydroxy-1,1-dimethylethyl)amino]sulfonyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	669
2733	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-5-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide hydrochloride	633
2734	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide hydrochloride	629
2735	N <sup>1</sup> -butyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>1</sup> -methyl-5-(1,3-oxazol-2-yl)isophthalamide	619.4
2736	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dimethyl-5-(1,3-oxazol-2-yl)isophthalamide	577.3
2737	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -ethyl-5-(1,3-oxazol-2-yl)-N <sup>3</sup> -propylisophthalamide	619.4
2738	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropyl-5-(1,3-thiazol-2-yl)isophthalamide hydrochloride	645
2739	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[[1-(propylbutyl)amino]sulfonyl]propanamide	568
2740	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[[2R)-2-(hydroxymethyl)pyrrolidin-1-yl]sulfonyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	729

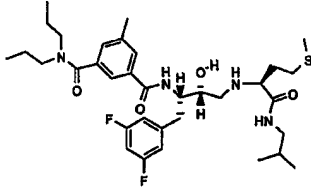
2741	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-5-[[2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	713
2742	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isobutylamino)propyl]-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide hydrochloride	571
2743	5-bromo-N <sup>1</sup> -{(1S,2R)-1-[3-fluoro-4-(trifluoromethyl)benzyl]-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	734.1
2744	5-bromo-N <sup>1</sup> -{(1S,2R)-2-hydroxy-1-(2,3,4-trifluorobenzyl)-3-[[3-(trifluoromethyl)benzyl]amino]propyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
2745	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2-ethylbutanoyl)-5-methylbenzamide hydrochloride	551.3
2746	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-[(2-propylpiperidin-1-yl)carbonyl]benzamide hydrochloride	606.3
2747	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-[(2-methylpyrrolidin-1-yl)carbonyl]benzamide hydrochloride	564.4
2748	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2,6-dimethylpiperidin-1-yl)carbonyl]-5-methylbenzamide hydrochloride	592.3
2749	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[[2-methoxyethyl)amino]sulfonyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	703
2750	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropyl-5-(1,3-thiazol-2-yl)isophthalamide dihydrochloride	689.6
2751	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-5-[[2-hydroxyethyl)amino]sulfonyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	685.2
2752	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-(2-propylpentanoyl)benzamide hydrochloride	579.3



2753	N <sup>1</sup> -(sec-butyl)-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>1</sup> -propylisophthalamide	594. 6
2754	N <sup>1</sup> -butyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>1</sup> -propylisophthalamide	594. 6
2755	N <sup>1</sup> -allyl-N <sup>1</sup> -cyclopentyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisophthalamide	600. 5
2756	N <sup>1</sup> ,N <sup>1</sup> -dibutyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisophthalamide	608. 6
2757	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -diisobutyl-5-methylisophthalamide	608. 6
2758	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-[(1Z)-prop-1-enyl]benzyl)amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
2759	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-(ethylsulfonyl)benzyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	644. 2
2760	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[1-(3-iodophenyl)cyclopropyl]amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	704. 1
2761		561. 2
2762	N <sup>1</sup> -[(1S,2R)-3-[(1,1'-biphenyl-3-ylmethyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
2763	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-hydroxy-1-phenylpropyl)amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	593. 3
2764	N <sup>1</sup> -cyclohexyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>1</sup> ,5-dimethylisophthalamide	594. 6
2765	N <sup>1</sup> -cyclohexyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>1</sup> -ethyl-5-methylisophthalamide	606. 6

2766	N <sup>1</sup> -[(1S,2R)-3-{[3-(1-benzothien-2-yl)benzyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	684.5
2767	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl]-5-ethynyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	630.2
2768	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(thien-3-ylbenzyl)amino]propyl}]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	633.0
2769	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(5-methylthien-2-yl)benzyl]amino}propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	647.0
2770	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(pyridin-4-ylbenzyl)amino]propyl}]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	629.6
2771	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(4-methylthien-2-yl)benzyl]amino}propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	648.5
2772	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-{[3-(2,4-dimethoxypyrimidin-5-yl)benzyl]amino}-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	690.6
2773	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-{[3-(3,5-dimethylisoxazol-4-yl)benzyl]amino}-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	647.6
2774	N <sup>4</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-{[3-(ethylbenzyl)amino]-2-hydroxypropyl}]-6-methyl-N <sup>2</sup> ,N <sup>2</sup> -dipropylpyridine-2,4-dicarboxamide	581.3
2775	N <sup>1</sup> -[(1S,2R)-3-{[3-(cyclopropylamino)benzyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	607.3
2776	N <sup>1</sup> -[(1S,2R)-3-{[3-(cyclopropylamino)benzyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-ethynyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	617.3
2777	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(2-isobutyl-1,3-thiazol-5-yl)cyclopropyl]amino}propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	641.3

2778	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	659. 3
2779	methyl 3-({[(2R,3S)-4-(3,5-difluorophenyl)-3-({3-[(dipropylamino)carbonyl]-5-methylbenzoyl}amino)-2-hydroxybutyl]amino}methyl)phenyl(methyl)carbamate	639. 3
2780	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({3-[methyl(methylsulfonyl)amino]benzyl}amino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	659. 3
2781	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-({3-[(dimethylamino)sulfonyl]benzyl}amino)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	659. 3
2782	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	606. 3
2783	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{{(2-isobutyl-1,3-thiazol-5-yl)methyl}amino}propyl)-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	668. 2
2785	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)-5-ethynyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	618. 3
2786	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	608. 3
2787	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl)-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	647. 2
2788	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	661. 3
2789	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isobutylisoxazol-5-yl)cyclopropyl]amino}propyl)-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	678. 3

2790	$N^1$ -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{{[1-(3-isobutylisoxazol-5-yl)cyclopropyl]amino}propyl})-5-ethynyl- $N^3,N^3$ -dipropylisophthalamide	635. 2
2791	$N^1$ -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({3-[(methanesulfonyl)amino]benzyl}amino)propyl]-5-methyl- $N^3,N^3$ -dipropylisophthalamide	645. 2
2792	$N^1$ -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{{[1-(3-isobutylisoxazol-5-yl)cyclopropyl]amino}propyl})-5-methyl- $N^3,N^3$ -dipropylisophthalamide	625. 3
2793	$N^1$ -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl]-5-(1,3-oxazol-2-yl)- $N^3,N^3$ -dipropylisophthalamide	629. 2
2794	$N^1$ -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{{3-(trifluoromethyl)benzyl}amino}propyl)-5-(1,3-oxazol-2-yl)- $N^3,N^3$ -dipropylisophthalamide	673. 2
2795	$N^1$ -[(1S,2R)-3-[(3-cyanobenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl- $N^3,N^3$ -dipropylisophthalamide	577. 2
2796		649. 0
2797	$N^1$ -((1S,2R)-1-(3,5-difluorobenzyl)-3-{{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl})-5-(1,3-oxazol-2-yl)- $N^3,N^3$ -dipropylisophthalamide	655. 3
2799	$N^1$ -[(1S,2R)-1-(3,5-difluorobenzyl)-3-({3-[(1E)-hex-1-enyl]benzyl}amino)-2-hydroxypropyl]-5-methyl- $N^3,N^3$ -dipropylisophthalamide	634. 6
2800	$N^1$ -[(1S,2R)-3-{{3-[(5-acetylthien-2-yl)benzyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl}-5-methyl- $N^3,N^3$ -dipropylisophthalamide	676. 5
2801	$N^1$ -[(1S,2R)-3-[(3-allylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl- $N^3,N^3$ -dipropylisophthalamide	592. 6
2802	$N^1$ -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{{3-[(6-methoxypyridin-3-yl)benzyl]amino}propyl})-5-methyl- $N^3,N^3$ -dipropylisophthalamide	659. 6

2803	N <sup>1</sup> -[(1S,2R)-3-[[2-tert-butylpyrimidin-4-yl)methyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	610. 3
2804	N <sup>4</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl]-6-methyl-N <sup>2</sup> ,N <sup>2</sup> -dipropylpyridine-2,4-dicarboxamide	595. 3
2805	N <sup>1</sup> -[(1S,2R)-3-[(3-butylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	608. 6
2806	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-pentylbenzyl)amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	622. 6
2807	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-pent-4-enylbenzyl)amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	620. 6
2808	N <sup>1</sup> -[(1S,2R)-3-[(3-cyclopentylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	620. 6
2809	N <sup>1</sup> -[(1S,2R)-3-[(3-cyclohexylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	634. 6
2810	N <sup>1</sup> -[(1S,2R)-3-[[3-(cyclohexylmethyl)benzyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	648. 6
2811	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-hex-5-enylbenzyl)amino]-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	634. 6
2812	methyl (2S)-3-[3-(((2R,3S)-4-(3,5-difluorophenyl)-3-((3-((dipropylamino)carbonyl)-5-methylbenzoyl)amino)-2-hydroxybutyl)amino)methyl)phenyl]-2-methylpropanoate	2812
2813	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(3-methylthien-2-yl)benzyl]amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	648. 5
2814	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(3-methylpyridin-2-yl)benzyl]amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	643. 6
2815	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(4-methylpyridin-2-yl)benzyl]amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	643. 6

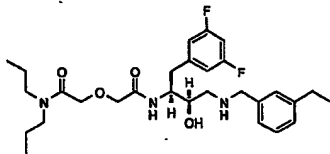
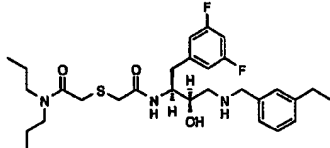
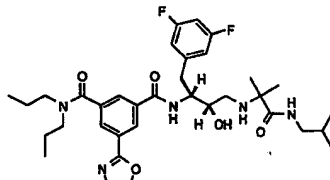
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2817	N <sup>1</sup> -[(1S,2R)-3-([3-(4-chlorobutyl)benzyl]amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	642.6
2818	N <sup>1</sup> -[(1S,2R)-3-([3-(3-cyanopropyl)benzyl]amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	619.6
2819	N <sup>1</sup> -[(1S,2R)-3-([3-(4-cyanobutyl)benzyl]amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	633.6
2820	N <sup>1</sup> -[(1S,2R)-3-([3-(6-cyanoethyl)benzyl]amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	661.6
2821	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([3-(6-methylpyridin-2-yl)benzyl]amino)propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	643.6
2822	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([3-(1,3-oxazol-2-yl)benzyl]amino)propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	619.2
2823	methyl 3-([((2R,3S)-4-(3,5-difluorophenyl)-3-([3-((dipropylamino)carbonyl)-5-(1,3-oxazol-2-yl)benzoyl]amino)-2-hydroxybutyl)amino)methyl]phenyl(methyl)carbamate	
2824	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([3-(1S)-1-((isobutylamino)carbonyl)-3-(methylsulfonyl)propyl]amino)propyl)-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	681.0
2825	N <sup>1</sup> -butyl-N <sup>3</sup> -{[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl]}-N <sup>1</sup> ,5-dimethylisophthalamide	580.3
2826	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)-1-methylethyl]amino)-2-hydroxypropyl)-5-([2-hydroxy-1,1-dimethylethyl]amino)sulfonyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	745.1

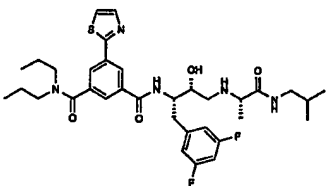
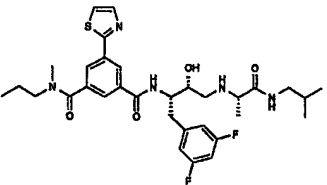
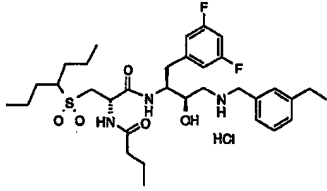
2827	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{methyl[(trifluoromethyl)sulfonyl]amino}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	727
2828	N <sup>1</sup> -[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-{[(2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	639
2829	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)-1-methylethyl]amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropyl-5-(1,3-thiazol-2-yl)isophthalamide	677. 1
2830	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[methyl(methylsulfonyl)amino]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	673. 2
2831	N <sup>1</sup> -butyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)-1-methylethyl]amino]-2-hydroxypropyl}-N <sup>1</sup> ,5-dimethylisophthalamide	594. 3
2832	N <sup>1</sup> -{(1S,2R)-1-(2,4-difluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	620. 2
2833	5-bromo-N <sup>1</sup> -{(1S,2R)-1-(2,4-difluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	684. 1
2834	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2-ethylpiperidin-1-yl)sulfonyl]propanamide	566
2835	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl}-5-ethynyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	616. 3
2836	N <sup>1</sup> -cyclobutyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisophthalamide	550. 1
2837	N <sup>1</sup> -cyclopentyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisophthalamide	564. 1
2838	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> -pentylisophthalamide	566. 1
2839	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -isopentyl-5-methylisophthalamide	566. 1

2840	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -ethyl-N <sup>3</sup> -(2-hydroxyethyl)-5-methylisophthalamide	568. 1
2841	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -(2-ethoxyethyl)-5-methylisophthalamide	568. 1
2842	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -(2-methoxyethyl)-N <sup>3</sup> ,5-dimethylisophthalamide	568. 1
2843	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -(2-furylmethyl)-N <sup>3</sup> ,5-dimethylisophthalamide	590. 1
2844	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[[ (2R,5R)-2,5-dimethylpyrrolidin-1-yl]carbonyl]-5-methylbenzamide	578. 1
2845	N <sup>1</sup> -cyclopentyl-N <sup>3</sup> -(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>1</sup> ,5-dimethylisophthalamide	578. 1
2846	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,5-dimethyl-N <sup>3</sup> -pentylisophthalamide	580. 1
2847	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -(2-hydroxyethyl)-5-methyl-N <sup>3</sup> -propylisophthalamide	582. 1
2848	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -ethyl-N <sup>3</sup> -(2-methoxyethyl)-5-methylisophthalamide	582. 1
2849	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> -(2-methylcyclohexyl)isophthalamide	592. 1
2850	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -(2-methoxyethyl)-5-methyl-N <sup>3</sup> -propylisophthalamide	596. 1
2851	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -bis(2-methoxyethyl)-5-methylisophthalamide	612. 1
2852	N <sup>1</sup> -allyl-N <sup>1</sup> -cyclohexyl-N <sup>3</sup> -(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisophthalamide	618. 1
2853	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipentylisophthalamide	636. 2



2854	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -bis(2-ethoxyethyl)-5-methylisophthalamide	640.1
2855	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-naphthylmethyl)amino]propyl}-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	655.2
2856	N <sup>1</sup> -butyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl}-N <sup>1</sup> ,5-dimethylisophthalamide	592.3
2857	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl}-5-[[2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	743.2
2860	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(3-hydroxypropyl)sulfonyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	688
2861	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1H-imidazol-4-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide trifluoroacetate	632
2862	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-isoxazol-3-yl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	633
2863	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[[2-(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl]-5-(1,3-oxazol-2-yl)benzamide	647
2864	N <sup>4</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-6-methyl-N <sup>2</sup> ,N <sup>2</sup> -dipropylpyridine-2,4-dicarboxamide	577.2
2865	N <sup>4</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl}-6-methyl-N <sup>2</sup> ,N <sup>2</sup> -dipropylpyridine-2,4-dicarboxamide	621.2
2866	N <sup>4</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl}-6-methyl-N <sup>2</sup> ,N <sup>2</sup> -dipropylpyridine-2,4-dicarboxamide	607.3
2867	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropyl-5-(1,3-thiazol-2-yl)isophthalamide	675.4

2868	$N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[methyl(thien-2-ylsulfonyl)amino]- $N^3,N^3$ -dipropylisophthalamide	741
2869	$N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-([[(2R)-2-hydroxypropyl]amino]sulfonyl)- $N^3,N^3$ -dipropylisophthalamide	703
2870	$N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[1-(2-isobutyl-1,3-thiazol-5-yl)cyclopropyl]amino]propyl}-5-(1,3-oxazol-2-yl)- $N^3,N^3$ -dipropylisophthalamide	694. 2
2871	$N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxy- $N^5,N^5$ -dipropylpentanediamide	548. 1
2872		534. 1
2873		550. 1
2874		656. 3
2875	$N$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(methylsulfonyl)methyl]benzamide	531
2876	$N$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-(2-methylpentanoyl)benzamide hydrochloride	551. 3
2877	$N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(methylsulfonyl)amino]- $N^3,N^3$ -dipropylisophthalamide	659. 2
2878	$N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide dihydrochloride	568

2879	$N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- $N^2$ -propionyl-3-[(1-propylbutyl)sulfonyl]-D-alaninamide	624
2880		658.3
2881		630.3
2882	$N^1$ -butyl- $N^3$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- $N^1$ -methyl-5-(1,3-thiazol-2-yl)isophthalamide	635.4
2883	$N$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(3-hydroxypropyl)(methylsulfonyl)amino]benzamide	590.2
2884	$N$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(methylsulfonyl)benzamide	517.2
2885	 as drawn	638
2886	$N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- $N^3,N^3$ -dipropyl-5-pyrimidin-2-ylisophthalamide	644
2887	$N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-([(2S)-2-hydroxypropyl]amino)sulfonyl)- $N^3,N^3$ -dipropylisophthalamide	703
2888	$N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- $N^3$ -methyl- $N^3$ -propyl-5-(1,3-thiazol-2-yl)isophthalamide	621.3
2889	$N$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2-methylpentanoyl)-5-(1,3-oxazol-2-yl)benzamide	604.3

2890	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({3-[(methylsulfonyl)amino]benzyl}amino)propyl]-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	698. 2
2891	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -(2,2-dimethylpropanoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	652
2892	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[[ (2R)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	743
2893	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(3-hydroxypropyl)(methylsulfonyl)amino]benzamide	590. 0
2894	N <sup>2</sup> -acetyl-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	610
2895	2-[allyl(methylsulfonyl)amino]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-thiazole-5-carboxamide	579. 2
2896	3-(butylsulfonyl)-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide bis(trifluoroacetate)	526
2897	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide bis(trifluoroacetate)	594
2898	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -isobutyryl-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	638

The compounds in the table immediately below were prepared essentially using the methods described above and  
5 illustrated below in the schemes.

The following compounds were named using the Advanced Chemistry Development Inc. (ACD) nomenclature program, IUPAC

Name Batch Version 4.5. The website for ACD is  
www.acdlabs.com.

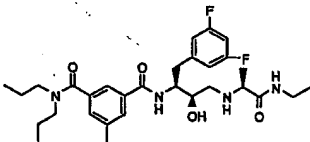
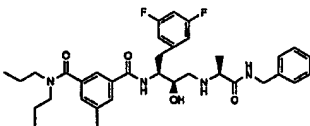
	Compound Name(s)	mass spec
2899	N-[(1S,2R)-3-(butylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-4-(ethylthio)benzamide	
2900	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1-(2-fluorophenyl)-5-oxopyrrolidine-3-carboxamide	540. 2
2901	N <sup>1</sup> -(4-tert-butyl-1,3-thiazol-2-yl)-N <sup>4</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)succinamide	
2902	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-hydroxy-6-(1-hydroxy-2,2-dimethylpropyl)pyridine-2-carboxamide	542. 3
2903	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-2-[[ethylamino]carbonyl]amino}benzamide	525. 3
2908	3-acetyl-N-[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]benzamide	
2909	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)amino]propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
2913	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,2-dioxido-3,4-dihydro-1,2-benzoxathiin-4-yl)amino]-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
2916	N <sup>1</sup> -[(1S,2R)-1-[[5-(cyanomethyl)-1H-imidazol-1-yl]methyl]-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
2918	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethylpyrimidin-4-yl)methyl]amino]-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
2920	N <sup>1</sup> -[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-5-[[ethyl(methyl)amino]sulfonyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	687. 3

2921	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2-hydroxyethyl)(methylsulfonyl)amino]benzamide	575. 9
2922	5-bromo-N <sup>1</sup> -{(1S,2R)-1-(2,4-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	646. 4
2923	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2-methoxyethyl)(methylsulfonyl)amino]benzamide hydrochloride	590. 0
2924	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(methylsulfonyl)methyl]benzamide	531. 2
2925	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(4-hydroxybutyl)sulfonyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide hydrochloride	702. 4
2926	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(dipropylamino)isoquinoline-7-carboxamide	589. 4
2927	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[[2-hydroxyethyl(methyl)amino]sulfonyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	703. 4
2928	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(ethylamino)sulfonyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	673. 4
2929	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(5-methyl-1,2,4-oxadiazol-3-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide hydrochloride	648. 4
2930	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxamide	
2931	3-(butylsulfonyl)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}propanamide	511
2932	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylmalonamide	
2933	N <sup>2</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylbicyclo[2.2.1]hept-5-ene-2,3-dicarboxamide	
2934	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylcyclopentane-1,3-dicarboxamide	

2935	N <sup>2</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dimethyl-N <sup>5</sup> ,N <sup>5</sup> -dipropylthieno[2,3-b]thiophene-2,5-dicarboxamide	
2936	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenyl-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide	
2937	N <sup>2</sup> -benzyl-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -[2-(dipropylamino)-2-oxoethyl]glycinamide	
2938	3-(4-chlorophenyl)-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide	
2939	(2E)-N <sup>5</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(methoxyimino)-N <sup>1</sup> ,N <sup>1</sup> -dipropylpentanediamide	
2940	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -[2-(dipropylamino)-2-oxoethyl]-N <sup>2</sup> -phenylglycinamide	
2941	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> ,N <sup>2</sup> -dipropylcyclohexane-1,2-dicarboxamide	
2942	N <sup>1</sup> -[(1S,2R)-3-[(benzyloxy)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
2943	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-phenylpropanamide	
2945	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1H-imidazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	632. 3
2946	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(1-hydroxy-2-propylpentyl)benzamide	567. 3
2947	N-{(1R,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-isobutyrylbenzamide hydrochloride	536. 2
2948	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2-propylpentanoyl)benzamide	565. 3
2949	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2-ethylbutanoyl)benzamide hydrochloride	537. 3

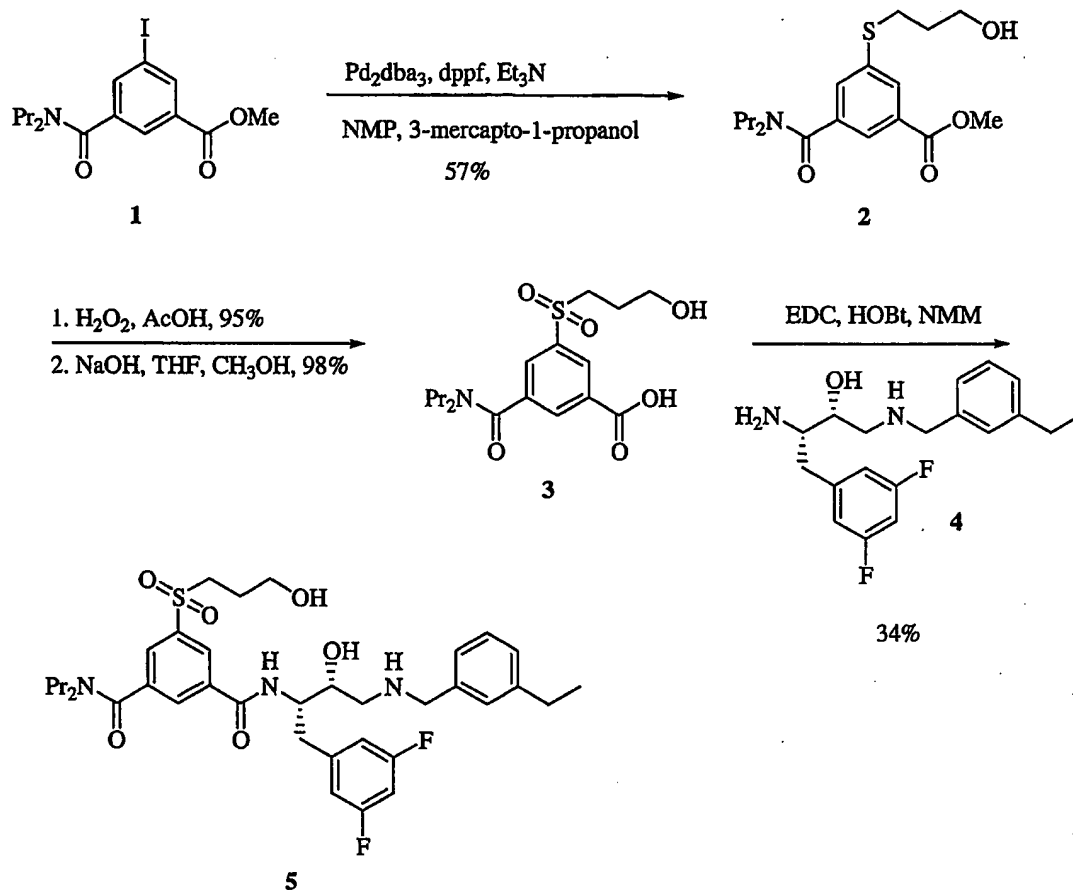
The compounds in the table immediately below were prepared essentially using the methods described above and illustrated below in the schemes.

The following compounds were named using the Advanced  
 5 Chemistry Development Inc. (ACD) nomenclature program, IUPAC Name Batch Version 4.5. The website for ACD is [www.acdlabs.com](http://www.acdlabs.com).

2951		561. 2
2953		623. 2
2954	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,3-dimethyl-N <sup>2</sup> ,N <sup>2</sup> -dipropylcyclopropane-1,2-dicarboxamide	558. 4
2956	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide	546. 5
2957	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,3-dimethyl-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide	560. 5
2958	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-ethyl-3-methyl-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide	574. 5
2959	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxy-3-methyl-N <sup>5</sup> ,N <sup>5</sup> -dipropylpentanediamide	562. 5
2960	2-[allyl(methylsulfonyl)amino]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-oxazole-4-carboxamide	563. 2
2962	N <sup>1</sup> -[(1S,2R)-3-({2-[bis(2-hydroxyethyl)amino]ethyl)amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	593. 5
2963	N <sup>1</sup> -[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide dihydrochloride	



2964	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[4-(hydroxymethyl)-1,3-oxazol-2-yl]benzamide hydrochloride	536.3
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**EXAMPLE SP-131**

- 5 **Step 1:** A solution of iodide 1 (1.70 g, 4.36 mmol),  $\text{Pd}_2\text{dba}_3$  (80 mg, 0.087 mmol), dppf (193 mg, 0.349 mmol), and triethylamine (882 mg, 8.72 mmol) in *N*-methylpyrrolidine (10 mL) was degassed under nitrogen for 15 min. 3-Mercapto-1-propanol (402 mg, 4.36 mmol) was added and the reaction mixture was
- 10 heated at 60 °C for 2 h. The reaction mixture was cooled to room temperature and then partitioned between ethyl acetate and saturated sodium chloride. The organic layer was washed (2x) with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure.
- 15 Purification by flash column chromatography (silica, 1:1 hexanes/ethyl acetate) gave sulfide 2 (880 mg, 57%) as a yellow oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.00 (s, 1H), 7.85 (s, 1H), 7.50 (s, 1H), 3.92 (s, 3H), 3.77 (m, 2H), 3.47 (m, 4H),

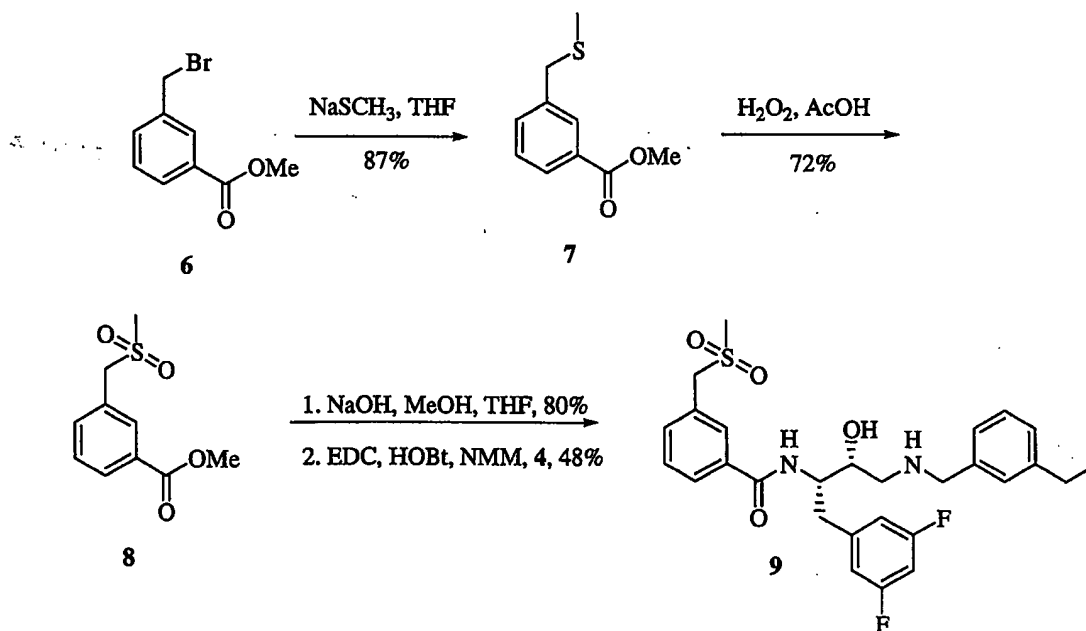
3.11 (m, 4H), 1.92 (m, 2H), 1.70 (m, 2H), 0.98 (m, 3H), 0.78 (m, 3H); ESI MS  $m/z$  354  $[M + H]^+$ .

**Step 2:** To a stirred solution of sulfide **2** (880 mg, 2.49 mmol) in 1:1 acetic acid/water (15 mL) was added excess 30% hydrogen peroxide. The reaction mixture was stirred overnight and then partitioned between ethyl acetate and water. The organic layer was washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a sulfone (912 mg, 95%) as a pale yellow oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.51 (s, 1H), 8.28 (s, 1H), 8.11 (s, 1H), 3.99 (s, 3H), 3.71 (m, 2H), 3.55 (m, 2H), 3.44 (m, 2H), 3.38 (m, 2H), 2.11 (m, 2H), 1.88 (m, 2H), 1.78 (m, 2H), 0.77 (m, 3H), 0.56 (m, 3H); APCI MS  $m/z$  387  $[M + H]^+$ .

**Step 3:** A solution of the sulfone from step 2 (912 mg, 2.36 mmol) in 3:1:1 methanol/tetrahydrofuran/1 N sodium hydroxide (20 mL) was stirred at room temperature for 2 h. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was acidified to pH 3 with 1 N hydrochloric acid and extracted with chloroform. The organic layer was dried (sodium sulfate), filtered, and concentrated to give acid **3** (860 mg, 98%) as a white foam:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.48 (s, 1H), 8.24 (s, 1H), 8.08 (s, 1H), 4.11 (m, 2H), 3.69 (m, 2H), 3.33 (m, 2H), 3.13 (m, 2H), 1.98 (m, 2H), 1.75 (m, 2H), 1.58 (m, 2H), 1.03 (m, 3H), 0.79 (m, 3H).

**Step 4:** To a stirred solution of acid **3** (630 mg, 1.69 mmol), amine **4** (688 mg, 1.69 mmol), HOBt (251 mg, 1.86 mmol), and *N*-methylmorpholine (855 mg, 8.45 mmol) in methylene chloride (15 mL) was added EDC (583 mg, 3.04 mmol). The reaction mixture was stirred overnight and then partitioned between ethyl acetate and water. The organic layer was washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and saturated

sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 93:7:1 methylene chloride/methanol/ammonium hydroxide) gave ALB 8198 (5) (400 mg, 34%) as a white solid: mp 62-66 °C; IR (ATR) 3293, 2964, 2874, 1614  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.18 (s, 1H), 8.06 (s, 1H), 7.85 (s, 1H), 7.28 (m, 2H), 7.15 (m, 2H), 6.85 (m, 2H), 6.62 (m, 1H), 4.31 (m, 1H), 3.79 (m, 2H), 3.67 (m, 2H), 3.55 (m, 2H), 3.24 (m, 2H), 3.05 (m, 2H), 2.91 (m, 4H), 2.86 (m, 1H), 2.60 (m, 2H), 1.95 (m, 2H), 1.73 (m, 2H), 1.56 (m, 2H), 1.22 (m, 3H), 1.03 (m, 3H), 0.72 (m, 3H); APCI MS  $m/z$  688  $[\text{M} + \text{H}]^+$ ; HPLC: Method A, 8.36 min (>99%, AUC). Anal. Calcd for  $\text{C}_{36}\text{H}_{47}\text{F}_2\text{N}_3\text{O}_6\text{S} \cdot 0.25\text{H}_2\text{O}$ : C, 62.45; H, 6.92; N, 6.07. Found: C, 62.21; H, 6.69; N, 5.97.

**EXAMPLE SP-132**

**Step 1:** A mixture of benzoate 6 (870 mg, 3.79 mmol) and sodium thiomethoxide (292 mg, 4.18 mmol) was stirred in THF (20 mL) at 40 °C. After 48 h, the reaction mixture was cooled to room

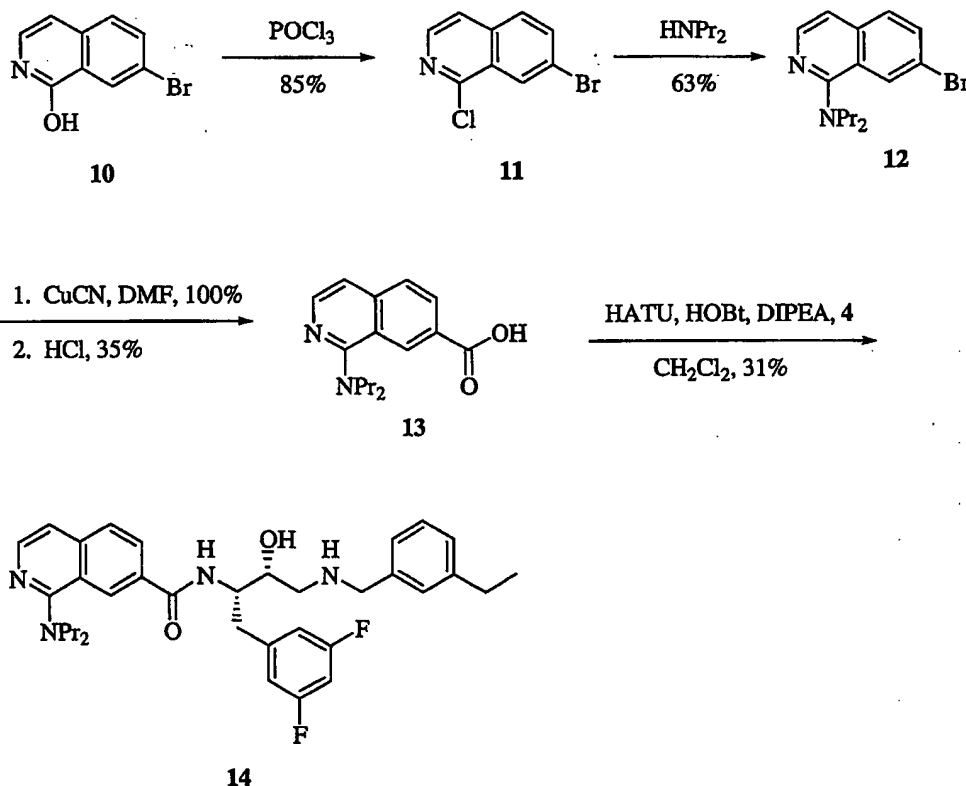
temperature and then partitioned between ethyl acetate and water. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to give sulfide **7** (650 mg, 87%) as a white foam:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (s, 1H), 7.88 (d,  $J = 8$  Hz, 1H), 7.40 (d,  $J = 8$  Hz, 1H), 7.27 (m, 1H), 3.92 (s, 3H), 3.71 (s, 2H), 1.99 (s, 3H).

**Step 2:** To a stirred solution of sulfide **7** (650 mg, 3.31 mmol) in 1:1 acetic acid/water (25 mL) was added excess 30% hydrogen peroxide. The reaction mixture was stirred overnight and then partitioned between ethyl acetate and water. The organic layer was washed with sodium bicarbonate, water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give sulfone **8** (540 mg, 72%) as a clear oil:  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.12 (s, 1H), 8.04 (d,  $J = 7$  Hz, 1H), 7.74 (d,  $J = 7$  Hz, 1H), 7.54 (m, 1H), 4.62 (s, 2H), 3.98 (s, 3H), 2.98 (s, 3H).

**Step 3:** A mixture of sulfide **8** (540 mg, 2.37 mmol) in 3:1:1 methanol/THF/2 N sodium hydroxide (10 mL) was stirred overnight. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was acidified to pH 3 with 1 N HCl and extracted with chloroform. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide an acid (406 mg, 80%) as a white solid:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.02 (s, 1H), 7.96 (d,  $J = 7$  Hz, 1H), 7.64 (d,  $J = 7$  Hz, 1H), 7.57 (m, 1H), 4.59 (s, 2H), 2.92 (s, 3H).

**Step 4:** To a stirred solution of acid from step 3 (260 mg, 1.21 mmol), HOBt (163 mg, 1.21 mmol), amine **4** (495 mg, 1.21 mmol), and *N*-methylmorpholine (612 mg, 6.05 mmol) was added EDC (418 mg, 2.18 mmol). The reaction mixture was stirred

overnight and then partitioned between ethyl acetate and water. The organic layer was washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 93:7:1 methylene chloride/methanol/ammonium hydroxide) gave ALB 8653 (**9**) (308 mg, 48%): mp 147-149 °C; IR (ATR) 3286, 2961, 1633, 1596 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.39 (d, *J* = 9 Hz, 1H), 7.77 (s, 1H), 7.72 (d, *J* = 7 Hz, 1H), 7.54 (d, *J* = 7 Hz, 1H), 7.48 (m, 1H), 7.18 - 6.93 (m, 7H), 5.03 (br s, 1H), 4.51 (s, 2H), 4.18 (br s, 1H), 3.68 (s, 2H), 3.67 (m, 1H), 3.12 (m, 1H), 2.91 (s, 3H), 2.88 (m, 1H), 2.61 (m, 1H), 2.45 (m, 2H), 2.43 (m, 2H), 1.13 (m, 3H); ESI MS *m/z* 531 [M + H]<sup>+</sup>; HPLC: Method A, 6.81 min (>99%, AUC). Anal. Calcd for C<sub>31</sub>H<sub>40</sub>F<sub>2</sub>N<sub>4</sub>O<sub>4</sub>•0.25H<sub>2</sub>O: C, 62.85; H, 6.12; N, 5.23. Found: C, 62.96; H, 5.83; N, 5.09.

**EXAMPLE SP-133**

**Step 1:** A solution of hydroxide **10** (2.5 g, 11.1 mmol) and POCl<sub>3</sub> (10.4 mL, 111 mmol) was stirred at 70 °C for 2.5 h. The  
5 reaction mixture was cooled to room temperature, poured into ice water and the solution was stirred overnight. The aqueous mixture was diluted with CHCl<sub>3</sub>, washed with a saturated solution of NaHCO<sub>3</sub>, saturated NaCl, dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure to afford chloride **11**  
10 (2.3 g, 85%) as a tan solid: <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.39-8.36 (m, 2H), 8.09-8.02 (m, 2H), 7.95 (d, J = 6 Hz, 1H).

**Step 2:** A solution of chloride **11** (500 mg, 2.1 mmol) and dipropylamine (2.8 mL, 21 mmol) was heated at 150 °C in a  
15 sealed tube for 2 d. The reaction mixture was cooled, and the solvent was removed under reduced pressure to provide amine **12** (400 mg, 63%) as a brown oil: <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.55 (s, 1H), 7.90 (d, J = 6 Hz, 1H), 7.75-7.64 (m, 2H), 6.87 (d, J = 6 Hz, 1H), 3.42 (q, J = 7 Hz, 4H), 1.65 (q, J = 7 Hz, 4H),  
20 0.94 (t, J = 7 Hz, 6H).

**Step 3:** A solution of amine **12** (350 mg, 1.1 mmol) and CuCN (204 mg, 2.2 mmol) in DMF (2 mL) was stirred at reflux for 24 h. The reaction mixture was cooled to room temperature,  
25 diluted with water, and extracted with EtOAc (3 x 50 mL). The combined organics were washed with saturated NaCl, dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure to provide a nitrile (279, mg, 100%) as a brown oil, which was used without any further characterization.

30

**Step 4:** A solution of the nitrile from step 4 (279 mg, 1.1 mmol) in concentrated HCl (4 mL) was heated at 150 °C in a sealed tube for 14 h. The reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure,

and the residue was dissolved in a 25%  $\text{NH}_4\text{OH}/\text{H}_2\text{O}$  solution and stirred for 1 h. The solution was acidified to pH 4, and extracted with  $\text{CHCl}_3$  (3 x 50mL). The combined organics were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated under reduced pressure to provide acid **13** (104 mg, 35%) as a white solid:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.85 (s, 1H), 8.15 (d,  $J$  = 8 Hz, 1H), 8.01 (d,  $J$  = 6 Hz, 1H), 7.79 (d,  $J$  = 7 Hz, 1H), 7.21 (d,  $J$  = 6 Hz, 1H), 3.47 (m, 4H), 1.68 (m, 4H), 0.83 (m, 6H); ESI MS  $m/z$  273  $[\text{M} + \text{H}]^+$ .

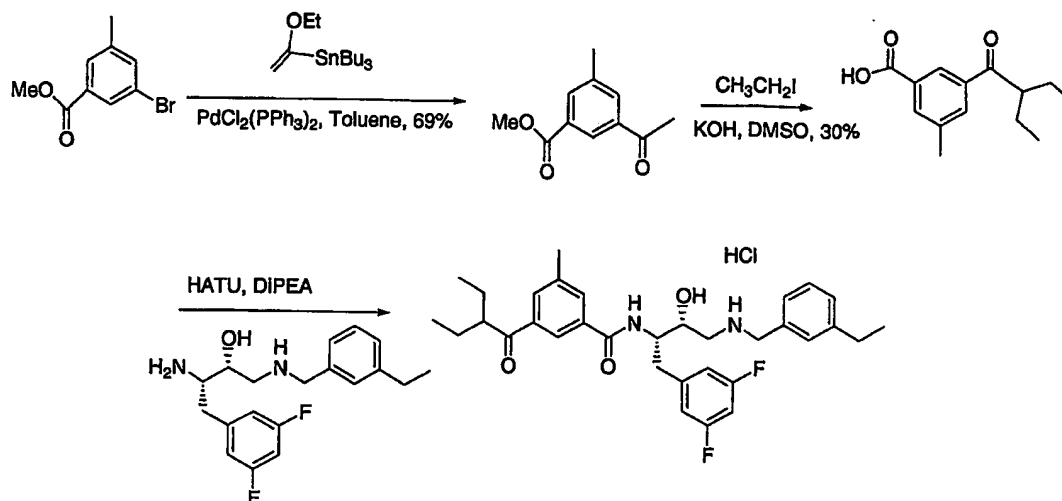
10

**Step 5:** To a stirred solution of acid **13** (103 mg, 0.38 mmol), amine **4** (154 mg, 0.38 mmol), HOBt (77 mg, 0.57 mmol), and DIPEA (0.2 mL, 1.1 mmol) in methylene chloride (4 mL) was added HATU (216 mg, 0.57 mmol). The reaction mixture was stirred overnight and then partitioned between methylene chloride and 1 N hydrochloric acid. The organic layer was washed with saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9:1 methylene chloride/methanol) gave a ALB 8655 (70 mg, 31): mp: 142-151  $^\circ\text{C}$ ; IR (ATR): 3222, 1621, 1585, 1114, 848, 700  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.46 (s, 1H), 9.09 (s, 2H), 8.57 (s, 1H), 8.35 (s, 1H), 8.09 (s, 1H), 7.29 (s, 1H), 7.46 (d,  $J$  = 6 Hz, 1H), 7.40 (s, 1H), 7.35 (d,  $J$  = 7 Hz, 1H), 7.27 (t,  $J$  = 7 Hz, 1H), 7.19 (d,  $J$  = 7 Hz, 1H), 7.04-6.97 (m, 3H), 4.24-4.08 (m, 4H), 3.73 (br s, 4H), 3.54 (br s, 8H), 3.18 (d,  $J$  = 8 Hz, 1H), 3.10 (br s, 1H), 3.00 (m, 1H), 2.87 (d,  $J$  = 8 Hz, 1H), 2.56-2.50 (m, 2H), 1.75 (d,  $J$  = 6 Hz, 4H), 1.12 (t,  $J$  = 7 Hz, 3H), 0.88 (t,  $J$  = 7 Hz, 6H); APCI MS  $m/z$  589  $[\text{M} + \text{H}]^+$ ; HPLC: Method A, 7.21 min (99%, AUC). Anal. Calcd for  $\text{C}_{35}\text{H}_{42}\text{F}_2\text{N}_4\text{O}_2 \cdot 2\text{HCl} \cdot 0.5\text{H}_2\text{O}$ : C, 62.68; H, 6.76; N, 8.35. Found: C, 62.60; H, 6.89; N, 8.29.

30

EXAMPLE SP-134





Ketones used in this EXAMPLE can be generally prepared as shown in chart U.

5

#### Step 1.

To a stirred solution of the halide (4.68 g, 20 mmol) in anhydrous toluene (10 mL) was added ( $\alpha$ -ethoxyvinyl)-  
 10 tributyltin (7.66 mL, 22 mmol) and dichlorobis(triphenylphosphine)palladium (0.715 g, 1 mmol). The reaction was heated under nitrogen at 100 °C for 14 hours. After hydrolysis of the reaction mixture with 1N HCl (100 mL), the organic layer was extracted with diethyl ether (100 mL x  
 15 2), washed with aqueous potassium fluoride (10%, 100 mL), dried with magnesium sulfate, and concentrated under vacuo. The crude product was purified by flash column chromatography (10 - 20% ethyl acetate: hexane) to afford 2.5 g of 3-Acetyl-  
 20 5-methyl-benzoic acid methyl ester as a white solid (65% yield). IR (drift) 3090, 3078, 3019, 2998, 2952, 2920, 1716, 1681, 1608, 1596, 1448, 1435, 1273, 1237, 1234, 1197, 1118, 893  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.44 (s, 1 H), 8.10 (s, 1 H), 8.01 (s, 1 H), 3.99 (s, 3 H), 2.68 (s, 3 H), 2.51 (s, 3 H); HRMS (FAB) calcd for  $\text{C}_{11}\text{H}_{12}\text{O}_3 + \text{H}^+ = 193.0865$ , found 193.0868.

25

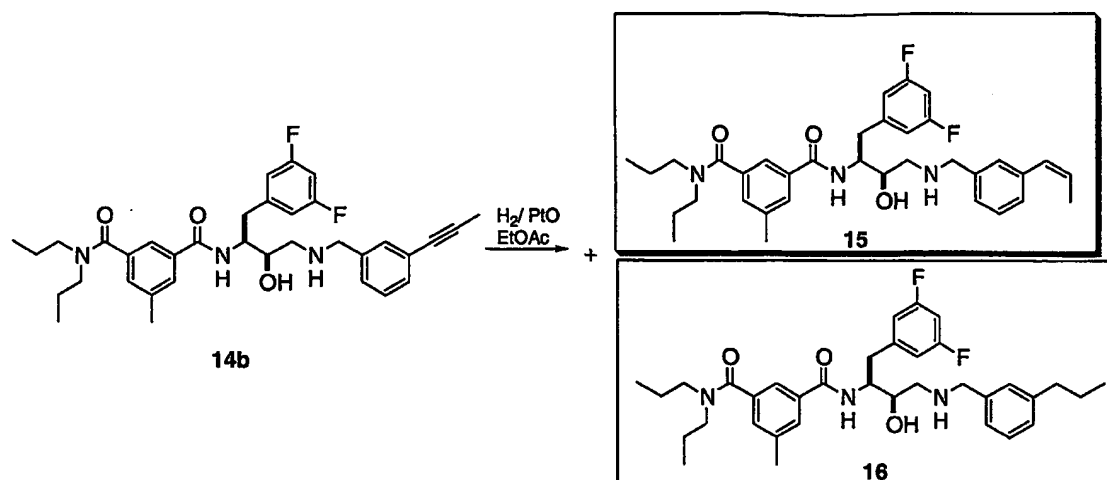
#### Step 2.

To a stirred suspension of potassium hydroxide (pellets) (5.0 g, 90.0 mmol) in dimethylsulfoxide (10 mL) was added 3-Acetyl-5-methyl-benzoic acid methyl ester (0.8 g, 4.5 mmol) and 1-iodopropane (2.9 mL, 36 mmol) at room temperature. The reaction mixture was heated to 50 - 60 °C and stirred for additional 1 hour. After cooled to room temperature, the reaction was poured into 1N aqueous HCl solution (100 mL). The aqueous solution was extracted with diethyl ether (80 mL x 2). The combined organic layer was washed with brine (80 mL x 2), dried with magnesium sulfate, and concentrated under vacuo. The crude product was purified by flash column chromatography (30 - 40% ethyl acetate: hexane) to afford 0.316 g of the benzoic acid as a pale yellow solid (30% yield).

### Step 3

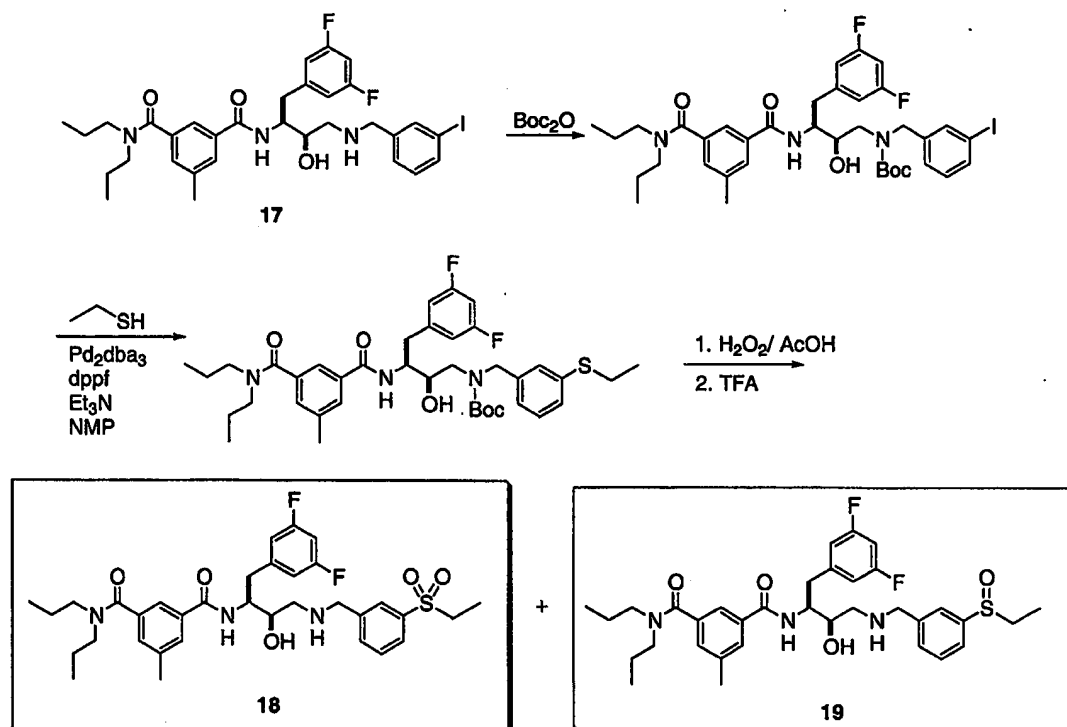
To a stirred solution of acid the benzoic acid (138.2 mg, 0.59 mmol) in DMF (3 mL) was added HATU (281 mg, 0.74 mmol), diisopropylethylamine (0.31 mL, 1.77 mmol), and then the amine (240 mg, 0.59 mmol) at room temperature. After stirred for 1 hour at room temperature, the reaction mixture was poured into 40 mL water. The aqueous solution was extracted with chloroform (50 mL x 2), and then organic layers were collected, washed with water (40 mL x 2), 1N HCl (40 mL x 2), sat. aq. sodium bicarbonate (40 mL x 2) and brine (40 mL x 2), dried over sodium sulfate, and concentrated under vacuo. The crude product was purified by flash column chromatography (10% methanol: dichloromethane) to afford 198 mg of the desired product as a pale yellow solid (61% yield).

### EXAMPLE SP-135



Compound **14b** (1 equiv, 0.064 mmol, 37.6 mg) was dissolved in EtOAc before the addition of PtO (catalytic) and an  $H_2$  balloon.

- 5 The reaction was stirred for 4 hours at ambient temperature before LC-MS determined the two products: **15** and **16**. The crude mixture was filtered through celite and the solvent was removed *in vacuo* before isolation by HPLC of each of the products: **15** (13 mg, 34 %,  $M+H^+ = 592.3$ ) and **16** (16 mg, 42 %,  $M+H^+ = 594.3$ ).
- 10

**EXAMPLE SP-136**

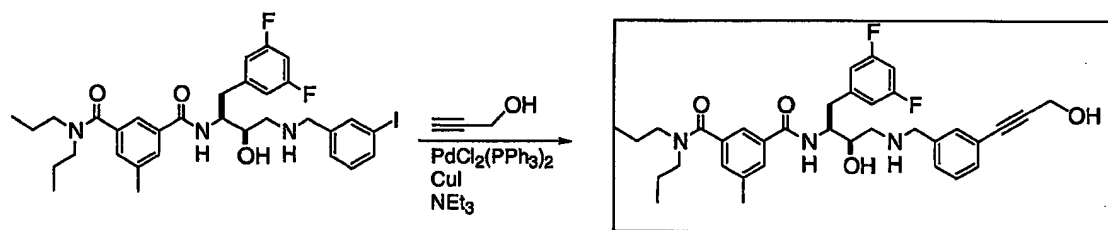
- Compound **17** (1 equiv, 0.46 mmol, 0.31 g) was dissolved in  $\text{CH}_2\text{Cl}_2$  and cooled to 0 °C before the addition of  $\text{Boc}_2\text{O}$  (1 equiv, 0.46 mmol, 0.1 g) and catalytic DMAP. After the reaction was judged to be done by TLC (4 h), the solvent was simply removed *in vacuo* and the product was used crude in the next step.
- The iodo compound (1 equiv, 0.13 mmol, 100 mg),  $\text{Pd}_2\text{dba}_3$  (0.02 equiv, 0.002 mmol, 2.4 mg), dppf (0.08 equiv, 0.01 mmol, 5.8 mg),  $\text{Et}_3\text{N}$  (2 equiv, 0.26 mmol, 0.04 mL), and NMP (0.3 M, 0.4 mL) were added to a sealed tube and flushed / bubbled with  $\text{N}_2$  (g) for 15 minutes. Ethanethiol was then added and the tube was sealed and stirred for 3h at 60 °C. At this point the reaction was cooled to ambient temperature, diluted with brine, and extracted 3x with EtOAc. The combined organic extracts were then washed with brine (2x), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and rotovapped to give the crude brown desired thioether. Column chromatography through  $\text{SiO}_2$  with 25 % EtOAc

in hexanes gave the purified product (71.5 mg, 0.1 mmol, 77 %).

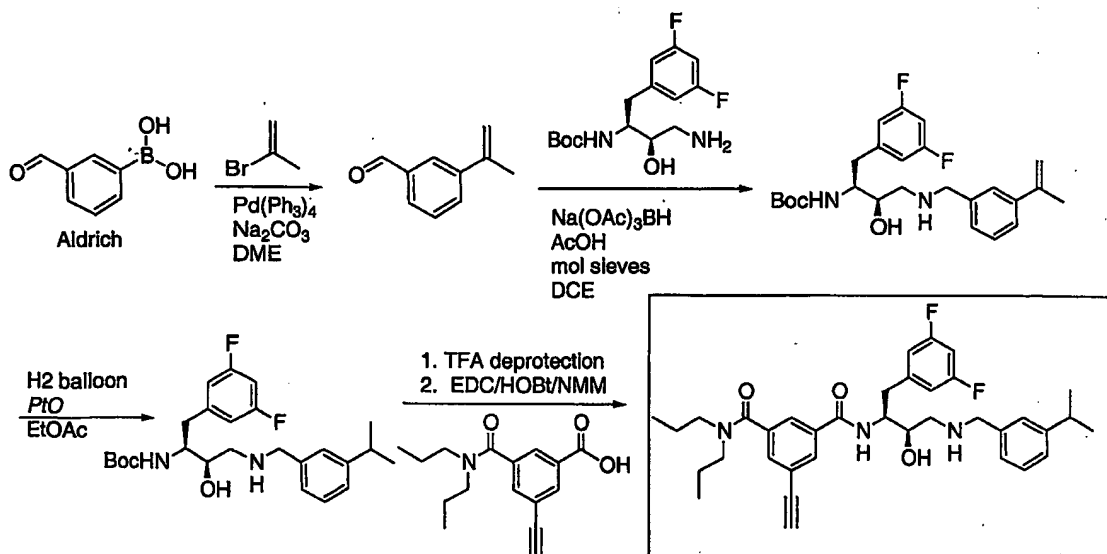
The thioether (1 equiv, 0.08 mmol, 56.3 mg) was dissolved in  
 5 AcOH (0.4 mL) and treated with 30 % H<sub>2</sub>O<sub>2</sub> (0.2 mL). The  
 reaction was stirred 2 h. At this point, the crude mixture  
 was partitioned between EtOAc and H<sub>2</sub>O, and the products were  
 extracted 3x with EtOAc. The organic extracts were dried over  
 Na<sub>2</sub>SO<sub>4</sub>, filtered, and rotovapped before column chromatography  
 10 purification through SiO<sub>2</sub> with 50 % EtOAc in hexanes gave the  
 separated Boc protected sulfone and sulfoxide. After TFA  
 deprotection and HPLC purification, the final products **18** (17  
 mg, 33%, M+H<sup>+</sup> = 644.2) and **19** (18 mg, 35 %, M+H<sup>+</sup> = 628.3) were  
 achieved.

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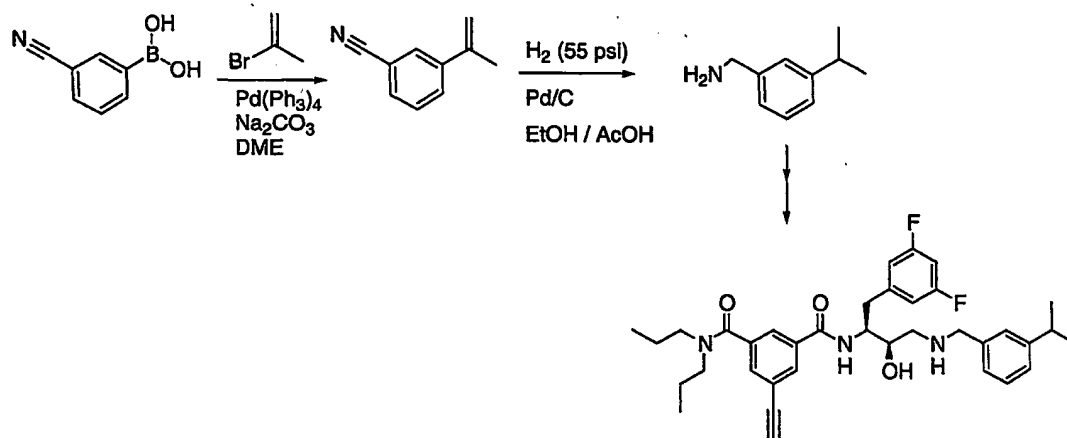
## EXAMPLE SP-137



## EXAMPLE SP-138

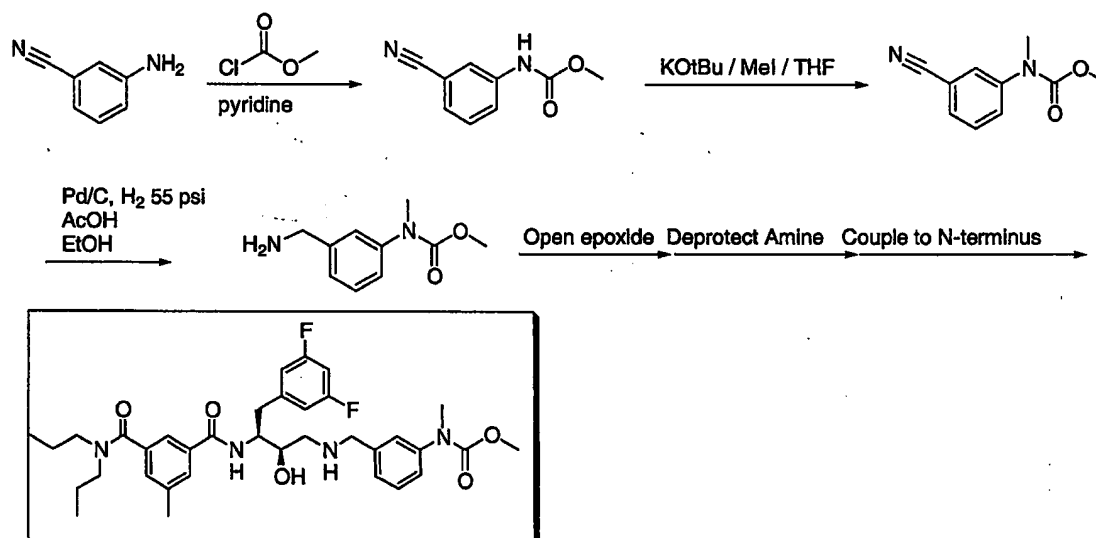


20

OR

5

## EXAMPLE SP-139



The aniline (1 equiv, 8.46 mmol, 1 g) was dissolved in  
 10 pyridine (1 M, 8.5 mL) and cooled to 0 °C before the addition  
 of methyl chloroformate (1.2 equiv, 10.2 mmol, 0.96 g, 0.78  
 mL). The reaction was allowed to warm to room temperature  
 overnight with stirring. The reaction mixture was then  
 rotovapped, and H<sub>2</sub>O was added to the residual oil, at which  
 15 point a white solid precipitated. The white precipitate was

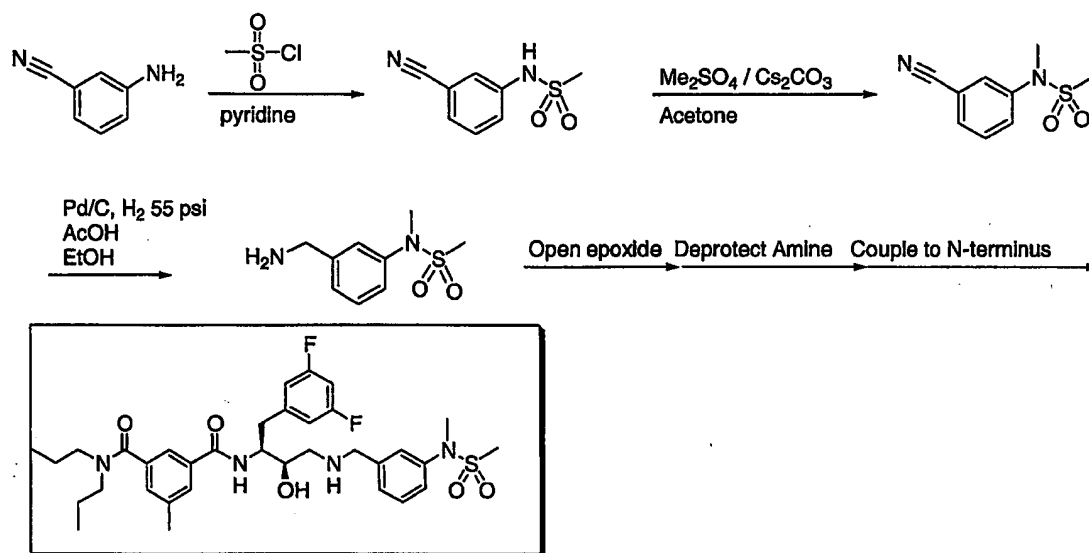
filtered and washed with H<sub>2</sub>O, and then dried on the vacuum pump overnight to give the clean crude carbamate (1.4 g, 93%)

The carbamate (1 equiv, 3.98 mmol, 0.70 g) was dissolved in  
5 THF (8 mL) and cooled to 0 °C before the addition of a 1M THF  
solution of KOtBu (1.1 equiv, 4.37 mmol, 4.37 mL). Upon  
addition of KOtBu, the starting material crashed out of  
solution, and so more THF was added (5 mL) along with dioxane  
(2 mL). At this point, despite the continued lack of  
10 solubility, MeI (1.1 equiv, 4.37 mmol, 0.62 g, 0.27 mL) was  
added and the reaction was allowed to warm to room temperature  
overnight with stirring. After 12 hours, the reaction was  
still not in solution, and TLC showed incomplete consumption  
of starting material. Thus, DMF (5 mL) was added and the  
15 reaction finally went into solution. After stirring for 5  
additional hours at ambient temperature, the reaction was  
complete. The crude reaction mixture was filtered through  
celite, rotovapped, partitioned between H<sub>2</sub>O and EtOAc,  
extracted 3x with EtOAc, and washed with brine. The organic  
20 extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and rotovapped.  
Purification through a short plug of SiO<sub>2</sub> with 30% EtOAc in  
hexanes gave the desired methylated carbamate which still  
contained a colored impurity which was undetected by TLC and  
NMR. (0.76 g, Quantitative)

25 The nitrile (1 equiv, 3.98 mmol, 0.76 g) was dissolved in  
ethanol, and N<sub>2</sub> (g) was bubbled through the solution for 5  
minutes before the addition of AcOH (1 equiv, 3.98 mmol, 2.27  
mL) and 5% DeGussa Pd/C (1 scoop). N<sub>2</sub> (g) was bubbled again  
30 for 5 minutes before shaking on Parr Shaker at 55 psi H<sub>2</sub>  
overnight. The reaction was filtered through celite and  
rotovapped to give the acetic acid salt of the desired  
product. The product was then partitioned between 10% NaOH

(aq) and 20% isopropanol / chloroform, and extracted 3x with 20% isopropanol / chloroform to give the desired free-base.

The crude free-base was used to open the epoxide. The M+H<sup>+</sup> mass  
5 of the final product is 639.3.

**EXAMPLE SP-140**

- 10 The aniline (1 equiv, 16.9 mmol, 2 g) was dissolved in  
pyridine and cooled to 0 °C before the addition of the sulfonyl  
chloride (1.5 equiv, 25.4 mmol, 2.91 g, 1.97 mL). Upon  
addition of the sulfonyl chloride, the reaction turned bright  
orange. The reaction was allowed to warm to room temperature  
15 overnight with stirring. After 12 hours, the reaction mixture  
was rotovapped, partitioned between CH<sub>2</sub>Cl<sub>2</sub> and NaHCO<sub>3</sub> (aq), and  
extracted 3x with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were  
washed with KHSO<sub>4</sub> (aq) and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered,  
and rotovapped to give the clean crude sulfonamide. (3.34 g,  
20 Quantitative)

The crude sulfonamide was dissolved in acetone before the  
addition of ground Cs<sub>2</sub>CO<sub>3</sub>, followed by Me<sub>2</sub>SO<sub>4</sub>. The Cs<sub>2</sub>CO<sub>3</sub> did  
not dissolve completely. The reaction was stirred overnight

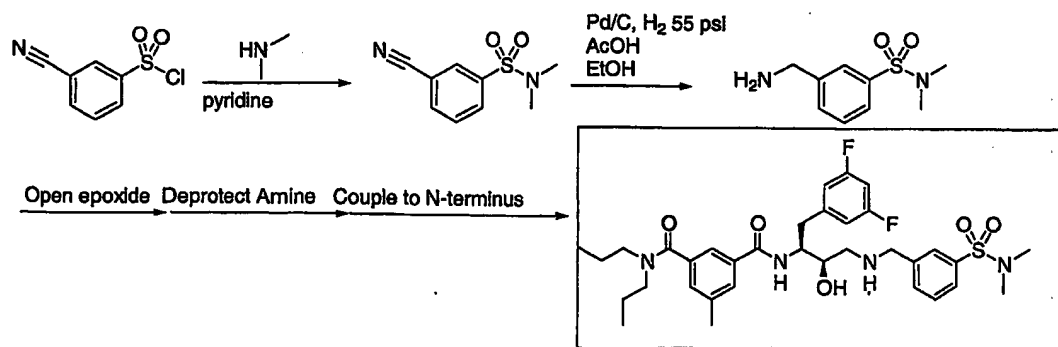


at ambient temperature. After 12 h, the brownish reaction mixture was rotovapped in a fume hood, partitioned between EtOAc and H<sub>2</sub>O, and extracted 3x with EtOAc. The combined organic extracts were then washed with NaHCO<sub>3</sub> (aq) and KHSO<sub>4</sub> (aq), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and rotovapped to give the crude methylated sulfonamide. By TLC the R<sub>f</sub> values of the starting sulfonamide and the final product were identical, however the spots were different colors. Quick purification through a plug of SiO<sub>2</sub> with 30% - 40% EtOAc in hexanes gave the desired product. (1.88 g, 93 %)

The nitrile (1 equiv, 8.94 mmol, 1.88 g) was dissolved in methanol, and N<sub>2</sub> (g) was bubbled through the solution for 5 minutes before the addition of AcOH (1 equiv, 8.94 mmol, 0.51 mL) and 5% DeGussa Pd/C (one scoop). N<sub>2</sub> (g) was bubbled again for 5 minutes before shaking on Parr Shaker at 55 psi H<sub>2</sub> for 2 hours. The reaction was filtered through celite and rotovapped to give the acetic acid salt of the desired product. The product was then partitioned between 10% NaOH (aq) and 20% isopropanol / chloroform, and extracted 3x with 20% isopropanol / chloroform to give the desired free-base.

The crude free-base was used to open the epoxide. The M+H<sup>+</sup> mass of the final product is 659.3.

#### EXAMPLE SP-141

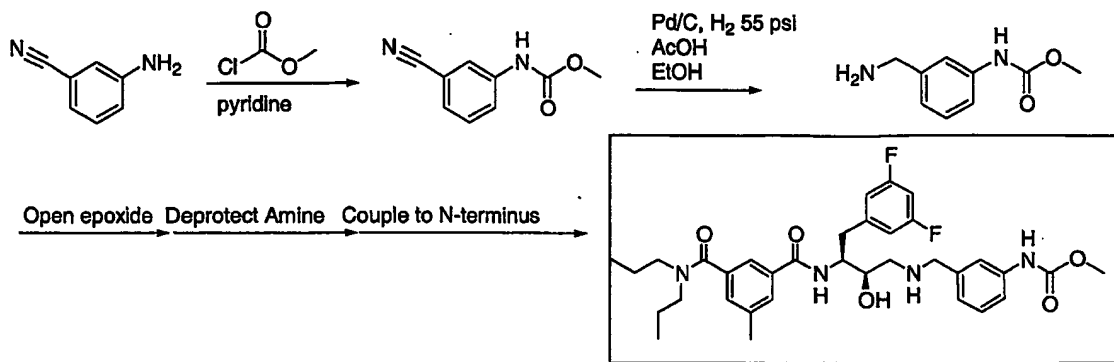


A 2M solution of dimethylamine in THF (1.2 equiv, 11.88 mmol, 5.94 mL) was dissolved in pyridine and cooled to 0 °C before the addition of the sulfonyl chloride (1 equiv, 9.9 mmol, 2 g). The reaction was allowed to warm to room temperature  
5 overnight with stirring. After 12 hours, the reaction mixture was rotovapped, partitioned between CH<sub>2</sub>Cl<sub>2</sub> and NaHCO<sub>3</sub> (aq), and extracted 3x with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed with KHSO<sub>4</sub> (aq) and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and rotovapped to give the clean crude sulfonamide. (2.04 g,  
10 98 %)

The nitrile (1 equiv, 9.7 mmol, 2.04 g) was dissolved in a mixture of ethanol, methanol, and THF until it finally went into solution. N<sub>2</sub> (g) was bubbled through the solution for 5  
15 minutes before the addition of AcOH (1 equiv, 9.7 mmol, 0.56 mL) and 5% DeGussa Pd/C (one scoop). N<sub>2</sub> (g) was bubbled again for 5 minutes before shaking on Parr Shaker at 55 psi H<sub>2</sub> overnight. The reaction was filtered through celite and rotovapped to give the acetic acid salt of the desired  
20 product. The product was then partitioned between 10% NaOH (aq) and 20% isopropanol / chloroform, and extracted 3x with 20% isopropanol / chloroform to give the desired free-base.

The crude free-base was used to open the epoxide. The M+H<sup>+</sup>  
25 mass of the final product is 659.3.

**EXAMPLE SP-142**

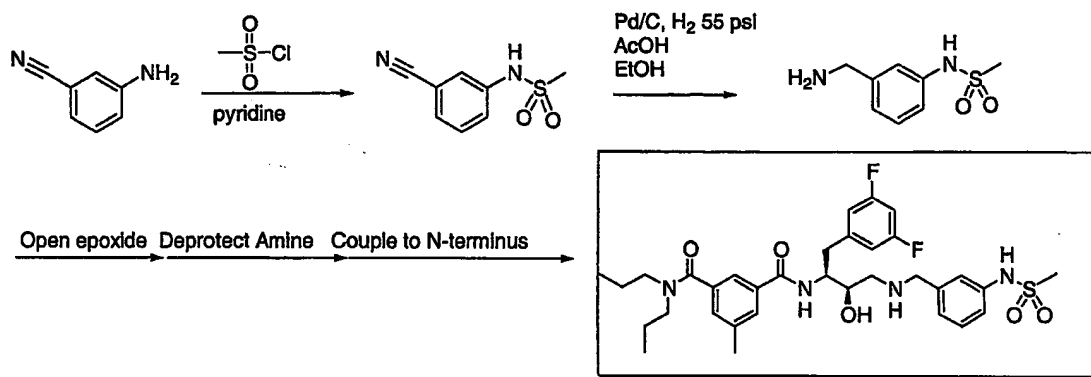


The aniline (1 equiv, 8.46 mmol, 1 g) was dissolved in pyridine (1 M, 8.5 mL) and cooled to 0 °C before the addition of methyl chloroformate (1.2 equiv, 10.2 mmol, 0.96 g, 0.78 mL). The reaction was allowed to warm to room temperature overnight. The reaction mixture was then rotovapped, and H<sub>2</sub>O was added to the residual oil, at which point a white solid precipitated. The white precipitate was filtered and washed with H<sub>2</sub>O, and then dried on the vacuum pump overnight to give the clean crude carbamate (1.4 g, 93%)

The nitrile (1 equiv, 3.43 mmol, 0.604 g) was dissolved in ethanol, and N<sub>2</sub> (g) was bubbled through the solution for 5 minutes before the addition of AcOH (1 equiv, 3.43 mmol, 0.2 mL) and 5% DeGussa Pd/C (one scoop). N<sub>2</sub> (g) was bubbled again for 5 minutes before shaking on Parr Shaker at 55 psi H<sub>2</sub> overnight. The reaction was filtered through celite and rotovapped to give the acetic acid salt of the desired product. The product was then partitioned between H<sub>2</sub>O with NH<sub>4</sub>OH and 20% isopropanol / chloroform, and extracted 3x with 20% isopropanol / chloroform to give the desired free-base.

The crude free-base was used to open the epoxide. The M+H<sup>+</sup> mass of the final product is 625.2.

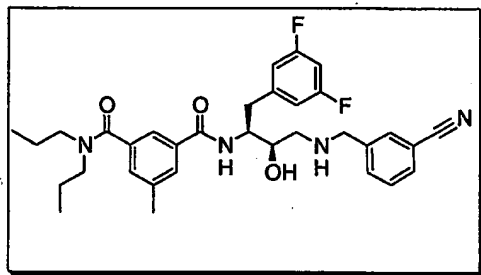
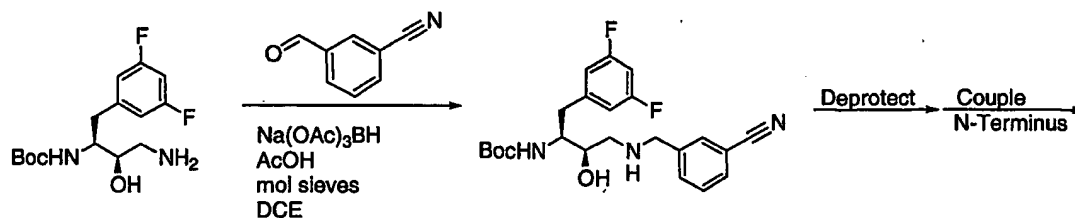
#### EXAMPLE SP-143



The aniline (1 equiv, 16.9 mmol, 2 g) was dissolved in pyridine and cooled to 0 °C before the addition of the sulfonyl chloride (1.5 equiv, 25.4 mmol, 2.91 g, 1.97 mL). Upon addition of the sulfonyl chloride, the reaction turned bright orange. The reaction was allowed to warm to room temperature overnight with stirring. After 12 hours, the reaction mixture was rotovapped, partitioned between  $\text{CH}_2\text{Cl}_2$  and  $\text{NaHCO}_3$  (aq), and extracted 3x with  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were washed with  $\text{KHSO}_4$  (aq) and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and rotovapped to give the clean crude sulfonamide. (3.34 g, Quantitative)

The nitrile (1 equiv, 7.40 mmol, 1.45 g) was dissolved in methanol, and  $\text{N}_2$  (g) was bubbled through the solution for 5 minutes before the addition of  $\text{AcOH}$  (1 equiv, 7.40, 0.42 mL) and 5% DeGussa  $\text{Pd/C}$  (one scoop).  $\text{N}_2$  (g) was bubbled again for 5 minutes before shaking on Parr Shaker at 55 psi  $\text{H}_2$  for 2 hours. The reaction was filtered through celite and rotovapped to give the acetic acid salt of the desired product. The product was then partitioned between  $\text{H}_2\text{O}$  with  $\text{NH}_4\text{OH}$  and 20% isopropanol / chloroform, and extracted 3x with 20% isopropanol / chloroform to give the desired free-base.

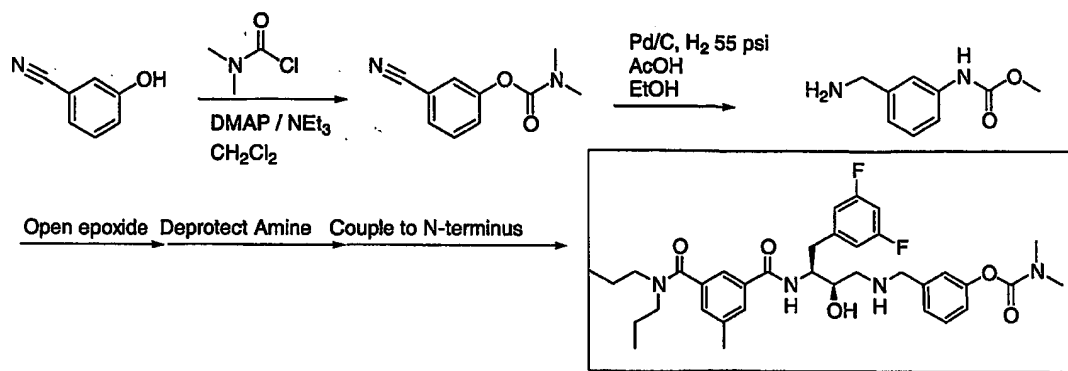
The crude free-base was used to open the epoxide. The  $\text{M}+\text{H}^+$  mass of the final product is 645.2

**EXAMPLE SP-144**

The aldehyde (1 equiv, 2.29 mmol, 0.3 g) and the amine (1.05  
 5 equiv, 2.40 mmol, 0.76 g) were dissolved in 1,2 dichloroethane  
 (40 mL) and treated with molecular sieves (a small scoop) and  
 a few drops of AcOH. The reaction was stirred for 1 h before  
 adding Na(OAc)<sub>3</sub>BH (1.3 equiv, 2.98 mmol, 0.63 g). The reaction  
 was stirred overnight at ambient temperature. After 12 h, the  
 10 reaction mixture was filtered, and rotovapped. The residue  
 was partitioned between EtOAc and H<sub>2</sub>O, and the product was  
 extracted 3x with EtOAc. The combined organic extracts were  
 dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and rotovapped to give the clean  
 crude desired amine. (Quantitative)

15 The crude material was deprotected with TFA and coupled to the  
 N-terminus as usual. The M+H<sup>+</sup> mass of the final product is  
 577.2.

20 **EXAMPLE SP-145**

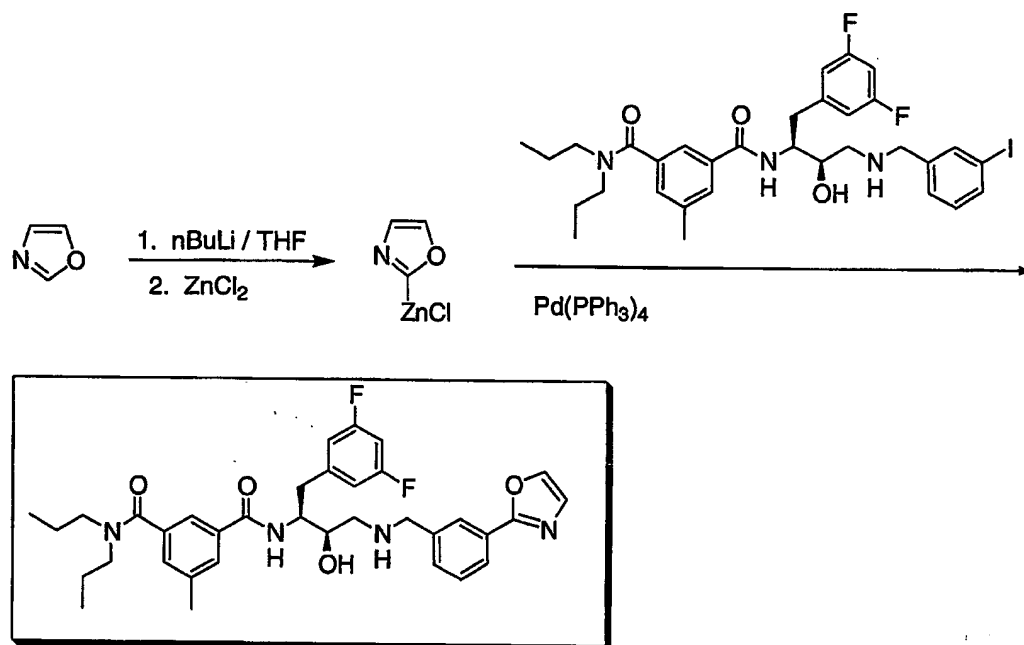


The phenol (1 equiv, 16.8 mmol, 2 g) was taken up in  $\text{CH}_2\text{Cl}_2$ , but did not dissolve, thus THF and acetone were added in a failed attempt to solubilize the phenol. The mixture was cooled to 0 °C before the addition of  $\text{NEt}_3$  (1 equiv, 16.8 mmol, 1.7 g, 2.3 mL), DMAP (1 equiv, 16.8 mmol, 2.05 g), and dimethylcarbamyl chloride (1 equiv, 16.8 mmol, 1.81 g, 1.55 mL). Upon addition of  $\text{NEt}_3$ , the reagents dissolved. The reaction appeared to be complete after stirring for 2 hours, as judged by TLC. However, the reaction was stirred for 2 days. After 2 days, the reaction was partitioned between  $\text{CH}_2\text{Cl}_2$  and  $\text{NaHCO}_3$  (aq), and extracted 3x with  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were washed with 1 N HCl and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and rotovapped to afford the clean crude carbamate. (3.04 g, 95%)

The nitrile (1 equiv, 16.0 mmol, 3.04 g) was dissolved in ethanol, and  $\text{N}_2$  (g) was bubbled through the solution for 5 minutes before the addition of 5% DeGussa Pd/C (one scoop).  $\text{N}_2$  (g) was bubbled again for 5 minutes before shaking on Parr Shaker at 55 psi for 1 hour. The reaction was filtered through celite and rotovapped to give the desired free-base.

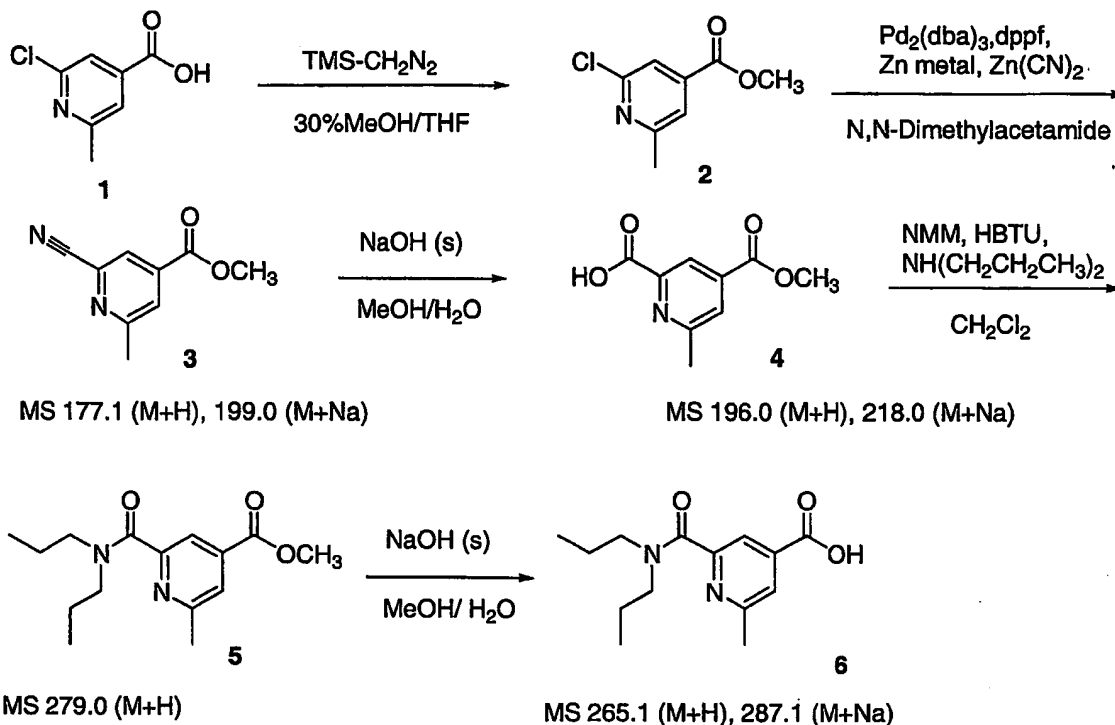
The crude free-base was used to open the epoxide. The  $\text{M}+\text{H}^+$  mass of the final product is 639.3.

## EXAMPLE SP-146



Oxazole (3.15 equiv, 1.89 mmol, 0.13 g) was weighed into an oven-dried round-bottom flask, dissolved in THF (3 mL), and cooled to -78 °C before the addition of a 1.6 M solution of nBuLi in hexanes (3.48 equiv, 2.09 mmol, 1.3 mL). After stirring for 30 minutes at -78 °C, a 1.0 M solution of ZnCl<sub>2</sub> in THF (9.06 equiv, 5.4 mmol, 5.4 mL) was added dropwise. At this point the stirring stopped due to increased viscosity or stickiness within the reaction vessel. This solution was warmed to 0 °C for 1 hour before the HCl salt of AN 104574-7 (1 equiv, 0.6 mmol, 0.429 g), along with Pd(PPh<sub>3</sub>)<sub>4</sub> were added. This mixture was heated to reflux for 1 hour. The reaction was then partitioned between EtOAc and H<sub>2</sub>O, extracted 3x with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and rotovapped. Chromatography on SiO<sub>2</sub> with 2 - 5% MeOH / CH<sub>2</sub>Cl<sub>2</sub> with a few drops of NH<sub>4</sub>OH yielded the clean desired product. (95%, 0.35 g, M+H<sup>+</sup> = 619.2)

EXAMPLE SP-147



### 2-Dipropylcarbamoyl-6-methyl-isonicotinic acid

- 5 A solution of 23.7 mmole (1.0eq.) of 2-chloro-6-methylisonicotinic acid in 32mL of 30%MeOH/THF was prepared. To the reaction mixture was added 30.0mmole (1.3eq) of (trimethylsilyldiazo)methane dropwise. The reaction was complete after stirring at rt overnight. A few drops of
- 10 glacial acetic acid were added to the reaction mixture prior to concentration by rotary evaporation to afford product **2**, quantitatively.
- To a dried 100 mL round bottom flask was added 22.0 mmole (1.0eq.) of the methyl ester **2**, 0.45mmole (0.02eq.)
- 15 tris(dibenzylideneacetone)dipalladium (0), 0.90 (0.04eq.) 1,1-bis(diphenylphosphine)ferrocene, 28.3mmole (0.13eq.) zinc metal dust and 10.7 (0.5eq) zinc cyanide. The reaction flask was flushed with nitrogen gas for 5 min and 45mL N,N-dimethylacetamide was added via syringe. The reaction was
- 20 complete after refluxing while stirring vigorously for 4 h. The reaction mixture was diluted with EtOAc (50mL) and washed



with 2N  $\text{NH}_4\text{OH}$  (3 x 50mL) followed by sat.  $\text{NaCl}$  (50 mL). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and vacuum filtered. The filtrate was concentrated by rotary evaporation and purified via column chromatography Hex/EtOAc (8:2) to  
5 yield product 3, 34% yield.

A solution of 1.2mmole (1.0eq.) of the nitrile 3 in 5 mL of methanol was prepared. To the reaction mixture was added 6.7mmole (5.7eq) of sodium hydroxide. After 1 h of stirring at rt, 5mL of  $\text{H}_2\text{O}$  were added to the reaction mixture. The reaction  
10 was complete after stirring for an additional 1.5h. The mixture was diluted with  $\text{CHCl}_3$  and washed with 2N  $\text{HCl}$ . The organic extracts were collected and dried over  $\text{Na}_2\text{SO}_4$  and vacuum filtered. The filtrate was concentrated by rotary evaporation to afford product 4, 61% yield.

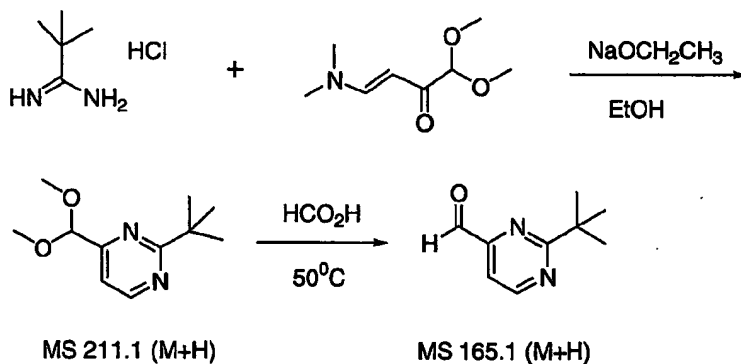
15 A solution of 0.7mmole (1.0 eq.) of the carboxylic acid 4 in 6mL of dichloromethane was prepared. To the reaction mixture was added 1.8mmole (2.6eq.) 4-methylmorpholine. The reaction flask was placed on ice to cool prior to addition of 0.8mmole (1.1eq.) HBTU and 0.8mmole (1.2eq.) dipropylamine. The  
20 reaction was complete after allowing to warm to rt overnight while stirring. The reaction mixture was diluted with EtOAc (25 mL) and washed with  $\text{H}_2\text{O}$  (2 x 25mL) followed by sat.  $\text{NaHCO}_3$  (2 x 25mL). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and vacuum filtered. The filtrate was concentrated by  
25 rotary evaporation to afford product 5, 64% yield.

A solution of 0.5 (1.0eq.) of the isophalate 5 in 2 mL of methanol was prepared. To the reaction mixture was added 4.5mmole (9.3eq) of sodium hydroxide. After 2 h of stirring at rt, 2mL of  $\text{H}_2\text{O}$  were added to the reaction mixture. The reaction  
30 was complete after stirring for an additional 1.5h. The mixture was diluted with EtOAc and washed with  $\text{H}_2\text{O}$  (2x) followed by sat.  $\text{NaHCO}_3$  (2x). The aqueous extracts were collected and acidified with conc.  $\text{HCl}$ . A solution of  $\text{CHCl}_3$ /iPA (1:3) was utilized for extraction. The organic extracts were

collected washed with sat. NaCl, dried over  $\text{Na}_2\text{SO}_4$  and vacuum filtered. The filtrate was concentrated by rotary evaporation to afford product **6**.

5

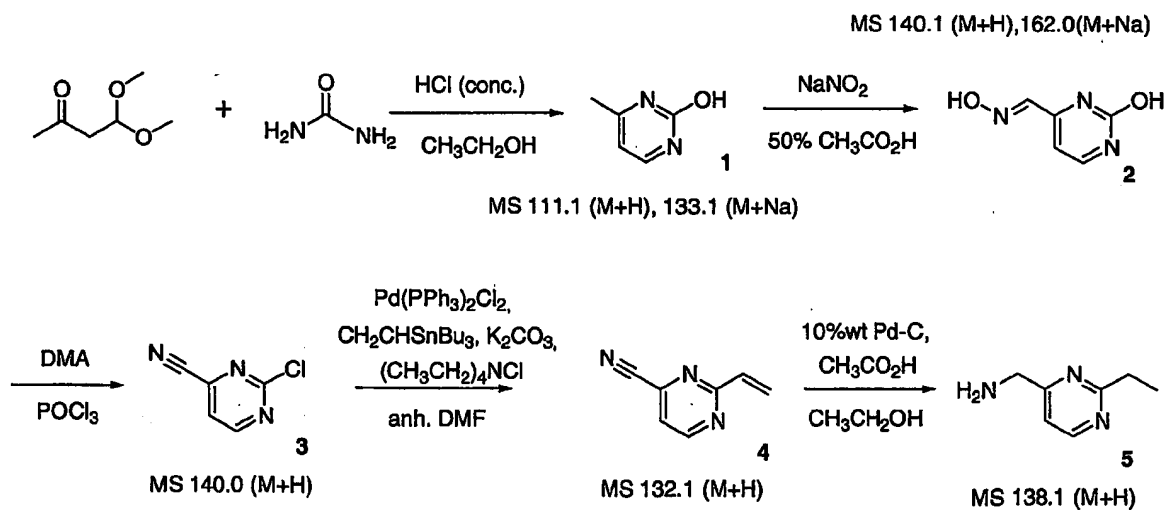
## EXAMPLE SP-148



10

Bredereck, H., Sell, R. and Effenberger, F.; *Chem. Ber.*; **1964**, 97, 3407.

## 15 EXAMPLE SP-149



**(2-Ethyl-pyrimidin-4-yl)-methylamine**

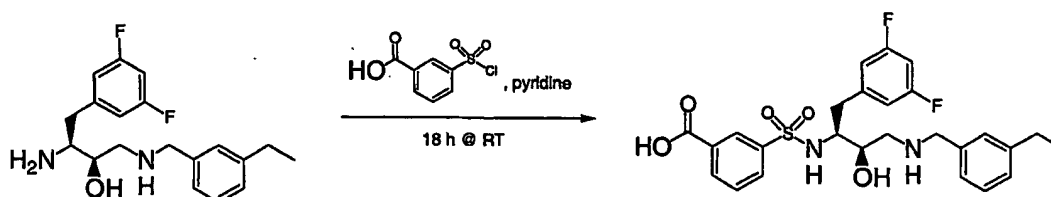
Experimental procedures were utilized in order to yield products 1 through 3 as described in the following references. Burness, D.M.; *J. Org. Chem.*, **1956**, 21, 97.

- 5 Daves, G.D., O'Brien, D.E., Lewis, L. and Cheng, C.C.; *J. Heterocycl. Chem.*, **1963**, 1, 130.

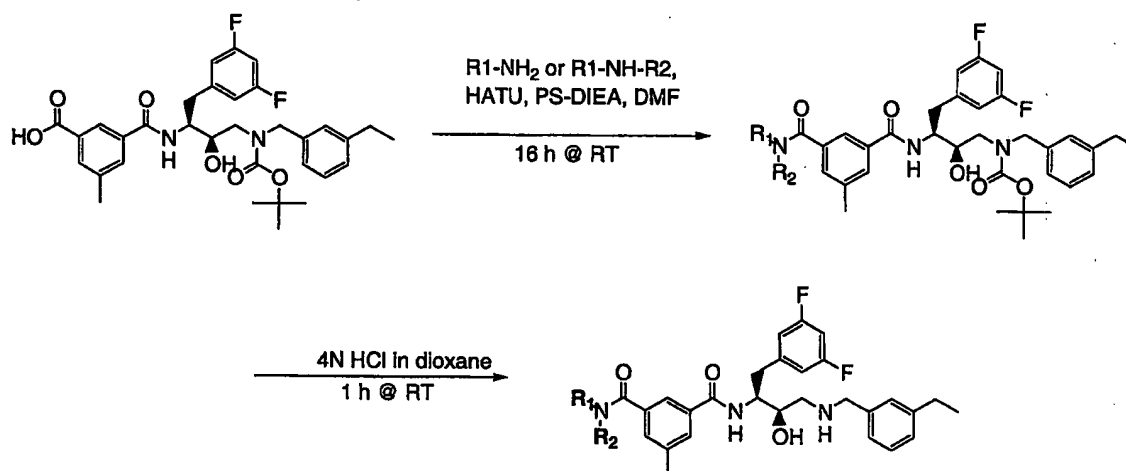
Into a oven-dried 50 mL round bottom flask was added 3.6mmole (1.0eq.) of the halopyrimidine 3, 5.4mmole (1.5eq.)  
10 tributyl(vinyl)tin, 0.09mmole (0.03eq.)  
bis(triphenylphosphine)palladium (II) chloride, 4.1mmole (1.1eq.) tetraethylammonium chloride, 3.8mmole (0.9eq.)  
potassium carbonate and 7.5 mL of dry DMF. The reaction was  
complete after refluxing under condenser with nitrogen inlet  
15 for 2 hrs. The reaction mixture was diluted with EtOAc (30 mL) and washed with H<sub>2</sub>O (2 x 30 mL) followed by sat. NaCl (30 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and vacuum filtered. The filtrate was concentrated by rotary evaporation, purified via column chromatography Hex/EtOAc (9:1) to yield  
20 product 4,  
42% yield.

In a small vial, a solution of 1.53mmole (1.0eq.) of the styrene 4 was prepared by dissolving in a minimal amount of  
25 EtOH. To the reaction mixture was added 0.1 mL of glacial acetic acid followed by a catalytic amount of 10%wt palladium on carbon. The reaction was complete after placement on the hydrogenator for 30 min. at 50psi. The reaction mixture was vacuum filtered through Celite and rinsed with EtOAc. The  
30 filtrate was concentrated by rotary evaporation to afford product 5.

## EXAMPLE SP-150

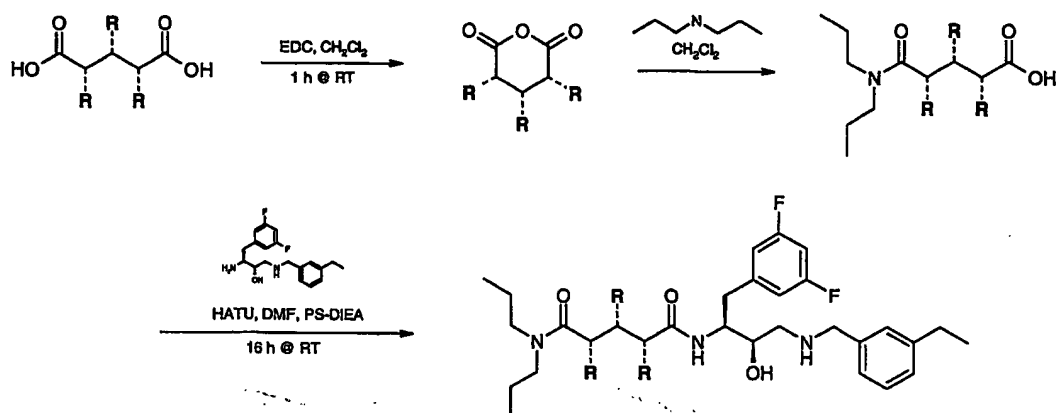


The starting diamine (~ 18 mgs, ~ 0.05 mmol) and 1 equiv. of sulfonyl chloride were dissolved in 1 ml of pyridine at - 5.0 °C in a 1-dram vial. This mixture was allowed to react for 18 hours. After reaction time, the pyridine was dissolved and the product mixture was prepared for LC-MS analysis using a Hewlett-Packard 1050 Series HPLC coupled to a Thermo-Finnigan LCQ Deca MS. From the LC-MS results, the final product was purified using the Varian Pro Star Preparative HPLC.

EXAMPLE SP-151 Synthesis of N-terminal dipropylamine replacement

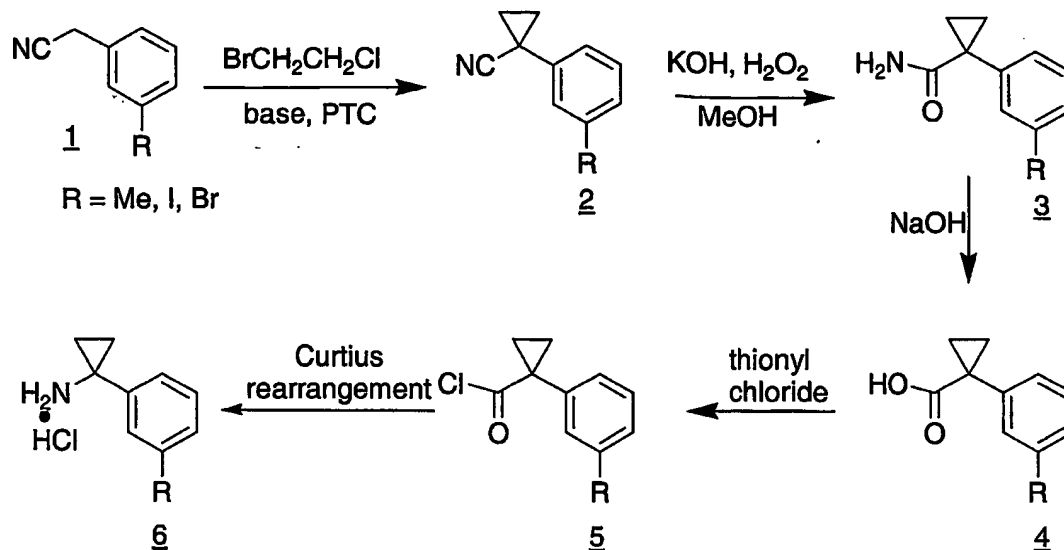
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EXAMPLE SP-152 Synthesis of N-terminal glutarates



From the 11 compounds that were made in this library, 2 were made with the starting dicarboxylic acid and the other 9 were already in the glutaric anhydride form. To prevent the dicarboxylic acids from forming diamides, 0.1 mmol of each acid was reacted with 1 equiv. of EDC in 1 ml of dichloromethane for 1 hour at room temperature. With all of the starting materials in the glutaric anhydride form, 0.1 mmol of each glutaric anhydride was mixed with 0.1 mmol of dipropylamine in 1.5 ml of dichloromethane for 2 hours at room temperature. The resulting acids were then reacted with 1 equiv. of the HEA piece using 1.1 equiv. of HATU as the coupling agent. 3 equiv. of polystyrene-bound diisopropylethylamine was used as the base. These reactions were run in 1.5 ml of DMF for 4 hours at room temperature. The products were then purified via the Varian Pro Star Preparative HPLC.

EXAMPLE SP-153: Representative procedure of CHART Y(R=I)



**Preparation of 1-arylcyclopropanecarbonitriles (2) (R = I)**

Org. Prep. Proc. Inter. 1995, 27(3), 355-59

5

To a vigorously stirred mixture of the iodobenzyl cyanide **1** (3g, 12.35 mM), benzyltriethylammonium chloride (TEBAC, 100 mg) and 1-bromo-2-chloroethane (BCE, 15 mL), 50% aq. NaOH solution (20 mL) was added dropwise over 35 min. (temp. 50°C). After addition, the reaction was stirred at 50°C for additional 2 hrs, then at RT for 2 hrs. Added water to 100 mL total and extracted with dichloromethane (3 x 25 mL). Organic extracts were washed with water, 5% aq. HCl, and water, then dried over  $\text{Na}_2\text{SO}_4$  and concentrated. Purified by Kugelrohr distillation. Yield **2** - 3.3 g (99%);  $\text{MH}^+(\text{CI})$  269.9.

**Preparation of amide 3.** A mixture of **2** (13.3 mM), 25% aq. KOH (0.34 mL), 30%  $\text{H}_2\text{O}_2$  (17.5 mL) and MeOH (100 mL) was heated at 55°C for 7 hrs. TLC showed no SM. The reaction mixture was concentrated and dried under vacuum. Yield 95%;  $\text{MH}^+(\text{CI})$  288.0.

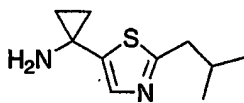
**Hydrolysis of 3.** An amide **3** (14 mM) was dissolved in a small amount of MeOH (5 mL) and 10% aq. NaOH solution (80 mL) and refluxed for 6 hrs. The mixture was cooled down and acidified with 15% HCl to pH~2. The solvent was partially

evaporated and white solid was collected by filtration. Yield of an acid 4 - 85%; MH+(CI) 288.9.

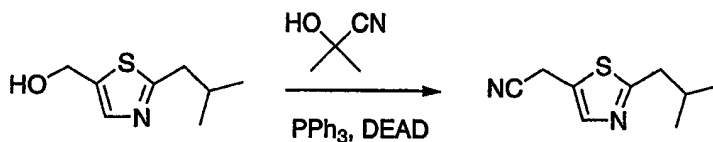
**Preparation of acid chloride 5.** The reaction mixture: acid 4 (8 mM) and thionyl chloride (2.0 g, 1.23 mL) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was heated o/n at 50°C (reflux). The next day a solvent was stripped on rotavapor and the residue was dried under vacuo. Used immediately without purification.

**Curtius rearrangement.** An acid chloride 5 (6.5 mM) was dissolved in acetone (15 mL), cooled to -10°C and treated with sodium azide (1.8 g in 5 mL of water). After stirring for 1 hr at -10°C the reaction mixture was poured into 100 mL of cold water and the azide was extracted into toluene. The toluene layer was washed with water and dried. The toluene solution was partially concentrated (to 15 mL) and the rest was carefully warmed to 100°C for 1 hr. Conc. HCl (8-10 mL) was added and the reaction mixture was refluxed for 15 min. with vigorous stirring. White crystals were decanted and dried under vacuo. Yield 84% of 6 (R = I); MH+(CI) 260.2.

EXAMPLE SP-154: Synthesis of 2-isobutyl-5-(1-

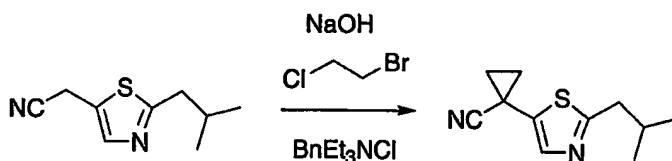


aminocycloprop-1-yl)thiazole:



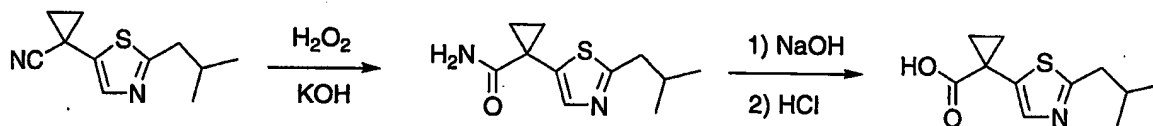
This procedure was adapted from: Wilk, BK. *Synth. Commun.* **1993**, 23, 2481-4. To a solution of the thiazole methyl alcohol (753 mg, 4.4 mmol) and triphenylphosphine (1.74 g, 6.63 mmol) in dry THF (10 mL) at 0 °C was added diethyl azodicarboxylate

(DEAD, 1.0 mL, 6.4 mmol) dropwise with stirring. After 10 min, acetone cyanohydrin (Aldrich, 0.6 mL, 6.6 mmol) was added dropwise with stirring. The resulting solution was stirred at 0 °C for 10 min, then at rt for 3 h, whereupon the mixture was concentrated under reduced pressure, and the residue purified by flash chromatography (EtOAc/hexanes elution; product  $R_f$  = 0.73 in 60% EtOAc/hexanes) to give a yellow oil (516 mg, 65%) as product.



10

This procedure was adapted from: *Org. Prep. Proc. Int.* **1995**, 27, 355-9. 50% Sodium hydroxide (aq, 5.0 mL total) was added to a solution of cyanide (516 mg, 2.9 mmol), 1-bromo-2-chloroethane (3.5 mL, 42 mmol), and benzyltriethylammonium chloride (25 mg, 0.09 mmol) at 50 °C. This was maintained at 50 °C for 2 h, then at rt for 2 h. Water was added such that the total volume was 20 mL, and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 10 mL). The combined organic extracts were washed (water, 1 N HCl, water), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc/hexanes elution) to give the product as an oil (403 mg, 68%);  $\text{MH}^+$  (CI) 207.1.

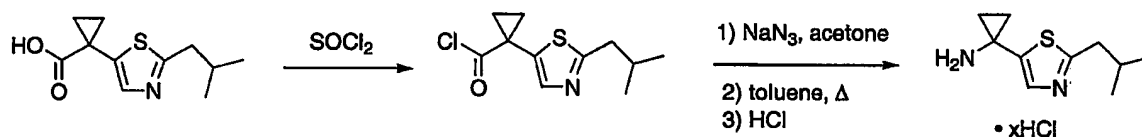


This procedure was adapted from: *Org. Prep. Proc. Int.* **1995**, 27, 355-9. Cyclopropylarylcyanide (403 mg, 1.96 mmol) was dissolved in MeOH (15 mL), and 30% hydrogen peroxide (2.7 mL) and 25% KOH (aq, 0.05 mL) were added at rt. The solution



was heated to 55 °C for 7 h. The reaction mixture was then concentrated in vacuo and stored in the freezer overnight. This crude product was used in the next reaction without further purification.

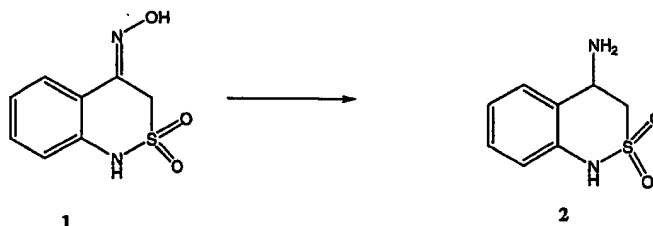
- 5 The crude amide was dissolved in minimal MeOH (1 mL), and 2.5 N NaOH (aq, 10 mL) was added. This suspension was heated to reflux (bath temp 105 °C) for 6 h, whereupon the mixture was cooled to 0 °C, and acidified to pH 3 using 3 N HCl (aq). This was partially concentrated, then extracted with CHCl<sub>3</sub>  
 10 (3x). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give a solid (189 mg, 43%); MH<sup>+</sup>(CI) 226.1.



- The carboxylic acid (189 mg, 0.84 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and thionyl chloride (0.2 mL, 2.7 mmol) was  
 15 added at rt. This was heated to reflux (bath temp 55 °C) for 3.5 h, whereupon the mixture was concentrated under reduced pressure. The crude acid chloride was dissolved in acetone (4 mL), and a solution of sodium azide (270 mg, 4.2 mmol) in water (1 mL) was added at -15 °C. After 1 h at -15 °C, water  
 20 (20 mL) was added, and the acyl azide was extracted into toluene (3x). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and partially concentrated (to ca. 30 mL). The solution was then warmed to 100 °C for 1 h. Conc. HCl (aq, 2 mL) was then added, and the mixture was heated to reflux for  
 25 15 min. The mixture was cooled to 0 °C, basified with 10 N NaOH (aq), then extracted with CHCl<sub>3</sub> (3x). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give an oil (R<sub>f</sub> = 0.37 in 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>; ninhydrin visualization); MH<sup>+</sup> (CI) 197.1.

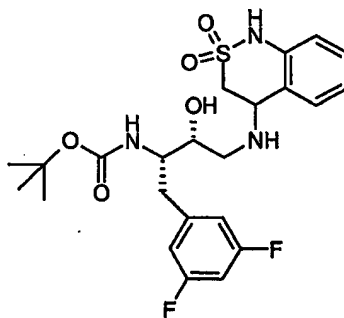
30

## EXAMPLE SP-155 Procedure A: Synthesis of 2 :

2,2-Dioxo-1,2,3,4-tetrahydro-2λ<sup>6</sup>-benzo[c][1,2]thiazin-4-ylamine

5 A solution of 0.58 g (2.7 mmol) of oxime 1 (prepared according to *J. Heterocyclic. Chem.* 17, 1281 (1980), the identical compound is described in this paper) in 13 ml of aqueous tetrahydrofuran (THF:H<sub>2</sub>O, 10:1) was stirred under argon atmosphere. Aluminum amalgam (from 0.52 g, 19 mmol, 7eq.  
 10 of Reynolds heavy-duty aluminum foil), prepared by sequential exposure (10-20 seconds each) of small strips to 1 N KOH, distilled water, 0.5% mercuric chloride, distilled water, and dry THF, was then added to the solution of 1 over a period of 3 hours. The reaction mixture was stirred overnight, then  
 15 filtered on a bed of celite and the solvent evaporated to yield 510 mg of 2 (94%) as an orange oil that slowly solidified. mass spec (CI) (MH<sup>+</sup>): 199.1

## EXAMPLE SP-155A



20

The compound of Example SP-155 can be used to open the appropriate boc protected amino epoxide to generate the compound of Example SP-155A. This compound can then be

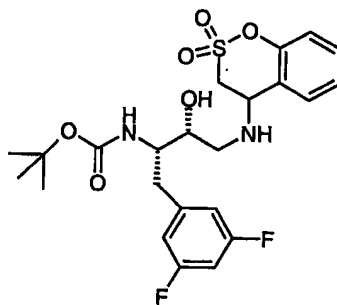
deprotected using methods well known in the art to generate the free amine, which can then be further manipulated.

EXAMPLE SP-156: Procedure B: Synthesis of 4,  
2,2-Dioxo-3,4-dihydro-2H-2λ<sup>6</sup>-benzo[e][1,2]oxathiin-4-ylamine



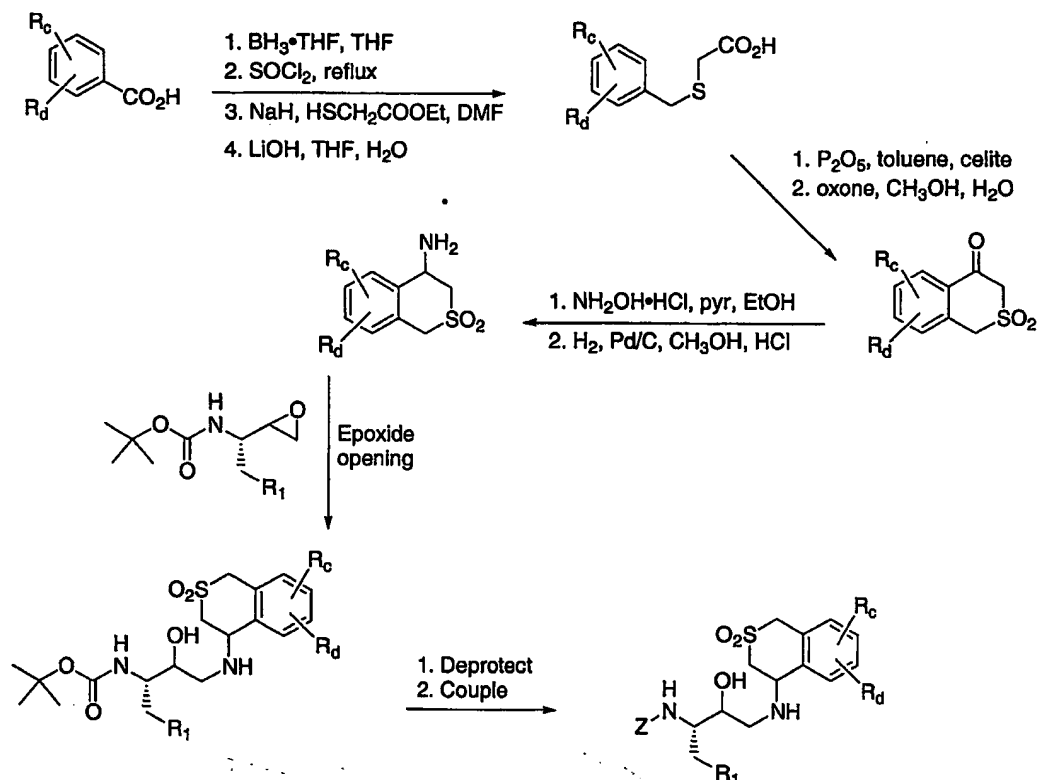
The amine 4 (mass spec (CI) (MH<sup>+</sup>): 200.0) was prepared according to the procedure A described above starting from 1H-2,1-Benzothiazin-4(3H)-one, oxime, 2,2-dioxide 3. Oxime 3 was obtained starting from commercially available 1,2-Benzoxathiin-4(3H)-one, 2,2-dioxide [49670-47-5].

EXAMPLE SP-156A:



The compound of Example SP-156 can be used to open the appropriate boc protected amino epoxide to generate the compound of Example SP-156A. This compound can then be deprotected using methods well known in the art to generate the free amine, which can then be further manipulated.

## EXAMPLE SP-156-B

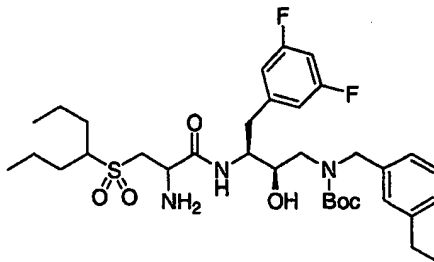


$\text{R}_\text{c}$  and  $\text{R}_\text{d}$  are independently H, halogen, alkoxy, or alkyl.  
 $\text{R}_1$  is 3,5-difluorophenyl; Z is residue from a group that will  
 couple to an amine, including, for example, carboxylic acid  
 derivatives (such as an isophthalamide), sulfonic acid  
 derivatives (such as para-toluenesulfonic acid), haloalkane  
 derivatives (such as iodopentane, and arylhaloalkyl  
 derivatives (such as benzylbromide.)

10

EXAMPLE SP-157: Preparation of : tert-butyl (2R,3S)-4-  
 (3,5-difluorophenyl)-2-hydroxy-3-({3-[(1-  
 propylbutyl)sulfonyl]alanyl}amino)butyl(3-  
 ethylbenzyl)carbamate

15



## Part A.

A 250 ml round bottom flask equipped with magnetic stir bar  
5 and N<sub>2</sub> inlet was charged with 5.0 g (34 mmole) methyl 2-  
acetamidoacrylate, 4.6 g (34 mmole) 4-mercapto heptane in 50  
ml methanol. The reaction vessel was charged with 3.6 g (36  
mmole) triethylamine and stirred at room temperature for 45  
minutes when HPLC indicated complete reaction. The reaction  
10 vessel was then treated with 47.2 g (77 mmole) Oxone. After  
90 minutes HPLC indicated complete oxidation to the desired  
sulfone. The reaction was filtered and concentrated *in vacuo*.  
The residue was partitioned between ethyl acetate and water  
and the organic layer was washed with brine, dried over sodium  
15 sulfate, and concentrated *in vacuo* to 9.2 g (86 %) of methyl  
N-acetyl-3-[(1-propylbutyl)sulfonyl]alaninate as a colorless  
oil. M + H = 308 g/m.

## Part B.

20

A 250 ml round bottom flask equipped with magnetic stir bar,  
reflux condenser, and N<sub>2</sub> inlet was charged with 9.2 g methyl N-  
acetyl-3-[(1-propylbutyl)sulfonyl]alaninate in 50 ml acetic  
acid and 50 ml conc. HCl. The solution was refluxed for 4  
25 hours then concentrated *in vacuo*. The residue was chased with  
toluene (2X ) then vacuum dried overnight to yield 7.8 g of  
the desired 3-[(1-propylbutyl)sulfonyl]alanine HCl salt.

## Part C.

30

A 250 ml round bottom flask equipped with magnetic stir bar and N<sub>2</sub> inlet was charged with 7.8 g (27 mmole) 3-[(1-propylbutyl)sulfonyl]alanine and 7.4 g (30 mmole) N-Cbz succinamide in 100 ml methylene chloride. The reaction was  
5 cooled to 0 °C, and 6.9 g NMM was added dropwise. The reaction was allowed to warm to room temperature and stirred for 4 hours at which point HPLC analysis indicated complete reaction. The reaction was concentrated *in vacuo* and partitioned between ethyl acetate and 1 N HCl. The organic  
10 layer was washed with water, brine, dried over sodium sulfate, and concentrated *in vacuo* to give 11.4 g of N-[(benzyloxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]alanine that was used without further purification. M + H = 386.

15 Part D.

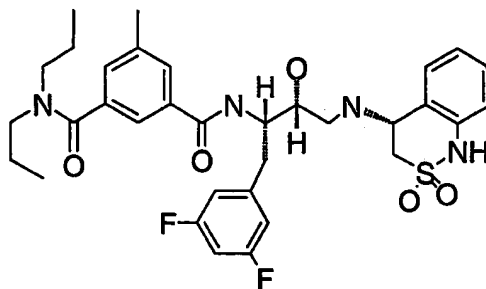
A 250 ml round bottom flask equipped with magnetic stir bar and N<sub>2</sub> inlet was charged with 4.0 g (10 mmole) N-[(benzyloxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]alanine and  
20 1.2 g (12 mmole) (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride in 50 ml anhydrous methylene chloride. To the reaction mixture was added 5.6 ml (51 mmole) NMM, 1.7 g (13 mmole) hydroxybenzotriazole, and lastly 3.1 g (16 mmole) 1-(3-  
25 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After stirring at room temperature for 3 hours, HPLC analysis indicated complete reaction. The reaction was diluted with methylene chloride and washed with saturated sodium bicarbonate solution, 0.5 M citric acid, and brine. The  
30 organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the N<sup>2</sup>-[(benzyloxy)carbonyl]-N<sup>1</sup>-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide. A 50 ml round bottom flask equipped with magnetic stir bar and N<sub>2</sub>

inlet was charged with the crude residue in anhydrous methylene chloride. The reaction was cooled to 0°C and added 2.5 g (12 mmole) di-tert-butyl dicarbonate and 1.2 ml (11 mmole) *N*-methyl morpholine. The reaction was allowed to warm  
5 to room temperature and stirred for 18 hours at which point HPLC analysis indicated complete reaction. The reaction was diluted with methylene chloride and washed with saturated sodium bicarbonate solution, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated in  
10 vacuo. The crude material was purified on silica gel by flash chromatography using a gradient solvent of 5-40% ethyl acetate in hexane to give 3.4 g of N<sup>2</sup>-[(benzyloxy)-carbonyl]-N<sup>1</sup>-{(1*S*,2*R*)- *N*-[(*t*-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-  
15 propylbutyl)sulfonyl]-D,L-alaninamide.  
M+Na = 824.

## Part E.

20 A Fisher-Porter bottle was charged with 3.4 g (4.2 mmole) of N<sup>2</sup>-[(benzyloxy)-carbonyl]-N<sup>1</sup>-{(1*S*,2*R*)- *N*-[(*t*-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-  
25 propylbutyl)sulfonyl]alaninamide in 50 ml methanol. After degassing with nitrogen, 1.6 g of 5% Pd/C (Degussa E101 50% water) was added. The reaction vessel was purged with 40 psi nitrogen (4X) then pressurized to 50 psi with hydrogen. After 15 minutes, HPLC analysis indicated complete reaction. The catalyst was removed by filtration through celite, and the  
30 filtrate concentrated in vacuo to give 2.4 g of N<sup>1</sup>-{(1*S*,2*R*)- *N*-[(*t*-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-  
propylbutyl)sulfonyl]-D,L-alanine. M+H = 668.

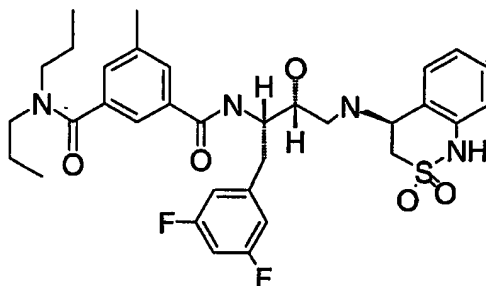
EXAMPLE SP-158



2,2-Dioxo-1,2,3,4-tetrahydro-2λ<sup>6</sup>-benzo[c][1,2]thiazin-4-ylamine

2 was prepared according to procedure A of EXAMPLE SP-155. Also, epoxide opening with 2 (see procedure A of EXAMPLE SP-155) was achieved according to the procedure described in Bennett, Frank. *Synlett* **1993**, 703-704. Mass spec (CI) MH<sup>+</sup> 643.7.

EXAMPLE SP-159



2,2-Dioxo-1,2,3,4-tetrahydro-2λ<sup>6</sup>-benzo[c][1,2]thiazin-4-ylamine

2 was prepared according to procedure A in EXAMPLE SP-155. Also, epoxide opening with 2 (see procedure A) was achieved according to the procedure described in Bennett, Frank. *Synlett* **1993**, 703-704. Mass spec (CI) MH<sup>+</sup> 643.7.

EXAMPLE SP-160

Synthesis of t-Boc-NH-di-F-Phe-Hydroxyethylamine(HEA)-O-Bn

To 2.4g (15 mmole, 3 eq.) of O-benzylhydroxylamine hydrochloride in 20 ml of EtOAc was added 20 ml of 1N KOH with stirring. The organic layer extracted and dried, stripping of solvent and reconstituted with 20 ml of DCM, 1.5 g (5 mmole) of

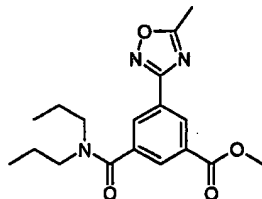


erythro-di-F-Phe-epoxide and 0.62 g (1mmole, 0.2 eq.) of Ytterbium(III) trifluoromethanesulfonate was added at room temperature. The mixture was stirred overnight and worked up by 1N HCl, bicarb and brine washings, dried, stripping of  
5 solvent gave 1.23 g crude which was subject to column purification, it afforded 0.76 g( 1.8 mmole, 36%) of the targeted compound as a pale white solid.

## EXAMPLE SP-161

10  $N^1$ -{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(5-methyl-1,2,4-oxadiazol-3-yl)- $N^3,N^3$ -dipropylisophthalamide hydrochloride

Step 1: Methyl 3-[(dipropylamino)carbonyl]-5-(5-methyl-1,2,4-  
15 oxadiazol-3-yl)benzoate



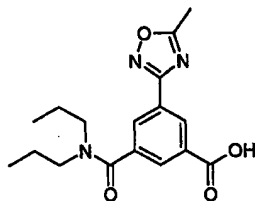
To a stirred solution of methyl 3-cyano-5-  
[(dipropylamino)carbonyl]benzoate prepared by the method in  
EXAMPLE S-2510 (2.3 g, 7.9 mmol) in methanol (26 mL) is added  
20 hydroxylamine hydrochloride (1.1 g, 16 mmol) and potassium carbonate (2.2 g, 16 mmol). The resulting reaction mixture is refluxed for 20 h, and then cooled to room temperature. The inorganic salts are filtered, and the filtrate is concentrated under reduced pressure to provide an amidoxime in quantitative  
25 yield.

To the amidoxime (1.3 g, 4 mmol), and EDC (1.5 g, 8 mmol) in 2-methoxyethyl ether (8 mL) is added acetic acid (0.21 mL, 4 mmol). The resulting reaction mixture is stirred for 24 h and then refluxed for 3 h. The reaction mixture is cooled to  
30 room temperature, diluted with ethyl acetate, washed with water, 1 N hydrochloric acid, saturated sodium bicarbonate,

and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl acetate hexanes) provides the title compound.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.69 (s, 1H),  
5 8.18 (m, 1H), 8.11 (s, 1H), 3.91 (s, 3H), 3.43 (t,  $J = 7$  Hz, 2H), 3.12 (t,  $J = 7$  Hz, 2H), 2.63 (s, 3H), 1.66 (t,  $J = 7$  Hz, 2H), 1.50 (t,  $J = 7$  Hz, 2H), 0.95 (t,  $J = 7$  Hz, 3H), 0.70 (t,  $J = 7$  Hz, 3H).

## 10 Step 2

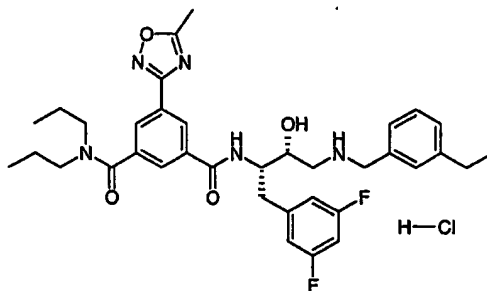
3-[(Dipropylamino)carbonyl]-5-(5-methyl-1,2,4-oxadiazol-3-yl)benzoic acid



A stirred solution of methyl 3-[(dipropylamino)carbonyl]-  
15 5-(5-methyl-1,2,4-oxadiazol-3-yl)benzoate (629 mg, 1.8 mmol) and lithium iodide (2.4 g, 18 mmol) in pyridine (7 ml) is refluxed for 18 h. The reaction mixture is cooled to room temperature and the solvent is concentrated under reduced pressure. The residue is dissolved in water, washed with  
20 ethyl acetate, the aqueous layer is acidified to pH 3 with 1 N hydrochloric acid and extracted with chloroform (3 x 100 mL). The organic layer is dried (sodium sulfate), filtered, and concentrated to give the title compound.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  11.11 (br s, 1H), 8.85 (t,  $J = 1$  Hz, 1H), 8.31 (t,  $J =$   
25 1 Hz, 1H), 8.23 (t,  $J = 1$  Hz, 1H), 3.51 (s, 2H), 3.19 (s, 2H), 2.72 (s, 3H), 1.73 (d,  $J = 7$  Hz, 2H), 1.56 (d,  $J = 7$  Hz, 2H), 1.01 (t,  $J = 7$  Hz, 3H), 0.76 (t,  $J = 7$  Hz, 3H).

## Step 3

$N^1$ -{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(5-methyl-1,2,4-oxadiazol-3-yl)- $N^3,N^3$ -dipropylisophthalamide hydrochloride



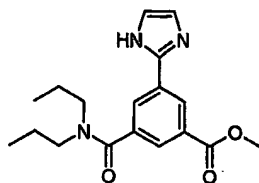
5        A solution of 3-[(dipropylamino)carbonyl]-5-(5-methyl-1,2,4-oxadiazol-3-yl)benzoic acid (209 mg, 0.63 mmol), HATU (359 mg, 0.95 mmol), HOBT (128 mg, 0.95 mmol), and diisopropylethylamine (165  $\mu$ L, 0.95 mmol) is stirred in methylene chloride (2.0 mL) for 15 min. A solution of  
10 (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method in EXAMPLE SP-272 (257 mg, 0.63 mmol) and diisopropylethylamine (165  $\mu$ L, 0.95 mmol) in methylene chloride (2.0 mL) is added and the reaction mixture is stirred  
15 overnight. The reaction mixture is diluted with methylene chloride, washed with 1 N hydrochloric acid (25 mL), saturated sodium bicarbonate (25 mL), and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9  
20 methanol/chloroform) provides the title compound as the free base. The solid is dissolved in methanol (1 mL), and treated with hydrochloric acid (0.3 mL of a 1.0 M solution in diethyl ether, 0.3 mmol). The resulting precipitate is collected by filtration to provide the title compound. APCI MS  $m/z$  648.4 [ $M$   
25 +  $H$ ] $^+$ .

EXAMPLE SP-162

$N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1H-imidazol-2-yl)- $N^3,N^3$ -dipropylisophthalamide

5 Step 1

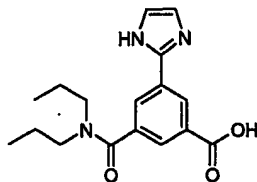
Methyl 3-[(dipropylamino)carbonyl]-5-(1H-imidazol-2-yl)benzoate



To a -70 °C stirred solution of 1-tert-butyl-  
 10 dimethylsilylimidazole (602 mg, 3.3 mmol) in tetrahydrofuran (10 mL) is added n-butyllithium (1.6 M in hexanes, 2.3 mL, 3.63 mmol). After 30 min, zinc chloride (1 M in diethyl ether, 9.9 mL, 9.9 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is then  
 15 added methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate prepared by the method in EXAMPLE SP-281, step2 (1.17 g, 3 mmol) followed by palladium(0) tetrakis(triphenylphosphine) (173 mg, 0.15 mmol). The reaction mixture is heated at reflux for 15 h. The reaction mixture is diluted with ethyl acetate  
 20 (50 mL), washed with water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 1-5% methanol/methylene chloride) provides the title compound in pure form. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.64 (s, 1H), 8.14 (s,  
 25 1H), 7.97 (s, 1H), 7.19 (s, 2H), 3.96 (s, 3H), 3.51 (m, 2H), 3.32 (m, 2H), 1.73 (m, 2H), 1.57 (m, 2H), 1.01 (m, 3H), 0.73 (m, 3H).

Step 2

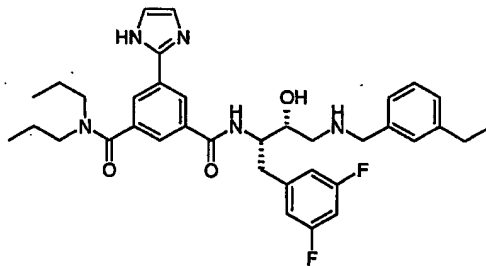
30 3-[(Dipropylamino)carbonyl]-5-(1H-imidazol-2-yl)benzoic acid



To a stirred solution of the ester from step 1 (260 mg, 0.79 mmol) in 2:1:1 tetrahydrofuran/methanol/water (8 mL) is added lithium hydroxide (140 mg, 3.3 mmol). The reaction mixture is stirred at room temperature for 2 h, and concentrated under reduced pressure. The residue is partitioned between water (10 mL) and diethyl ether (10 mL). The aqueous layer is acidified to pH 4 - 5 with 1 N hydrochloric acid and extracted with 3:1 chloroform/2-propanol (3 x 30 mL). The combined organic layers are dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide the title compound. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 8.64 (s, 1H), 8.10 (s, 1H), 8.01 (s, 1H), 7.28 (s, 2H), 3.52 (m, 2H), 3.26 (m, 2H), 1.75 (m, 2H), 1.59 (m, 2H), 1.02 (t, J = 7 Hz, 3H), 0.75 (t, J = 7 Hz, 3H).

### Step 3

N<sup>1</sup>-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1H-imidazol-2-yl)-N<sup>3</sup>,N<sup>3</sup>-dipropylisophthalamide



To a stirred solution of 3-[(dipropylamino)carbonyl]-5-(1H-imidazol-2-yl)benzoic acid (250 mg, 0.79 mmol), diisopropylethylamine (103 mg, 0.8 mmol), and HBTU (330 mg, 0.87 mmol) in methylene chloride (5 mL) is added a mixture of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-

ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (322 mg, 0.79 mmol) and diisopropylethylamine (206 mg, 1.6 mmol) in methylene chloride (5 mL). The reaction mixture is stirred at room temperature for 4 h and concentrated under reduced pressure. The residue is diluted with ethyl acetate (20 mL), washed with saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5:95 methanol/methylene chloride) provides the title compound in pure form. APCI MS  $m/z$  632.3  $[M + H]^+$ .

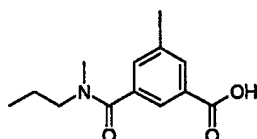
## EXAMPLE SP-163

$N^1$ -{(1S,2R)-1-Benzyl-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- $N^3$ -methyl-5-(1,3-oxazol-2-yl)- $N^3$ -propylisophthalamide

15

## Step 1

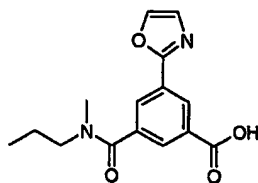
Methyl 3-iodo-5-[[methyl(propyl)amino]carbonyl]benzoate



To 3-iodo-5-(methoxycarbonyl)benzoic acid (1.0 g, 3.3 mmol), prepared as in EXAMPLE SP-281, step 1, and diisopropylethylamine (1.7 mL, 9.8 mmol) in DMF (10 mL) is added *O*-(7-Azabenzotriazol-1-yl)- $N,N,N',N'$ -tetramethyluronium hexafluorophosphate (HATU, 1.5 g, 3.9 mmol) then *N*-methylpropylamine (503  $\mu$ L, 4.9 mmol). The solution is stirred at room temperature 2 h. The solution is diluted in ethyl acetate and washed with water, saturated sodium bicarbonate, and brine. The organic layer is dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound in crude form. This material is purified by flash chromatography (40% ethyl acetate/hexane) to give the purified title compound. MS (ESI)  $[M+H]^+$  = 362.4.

## Step 2

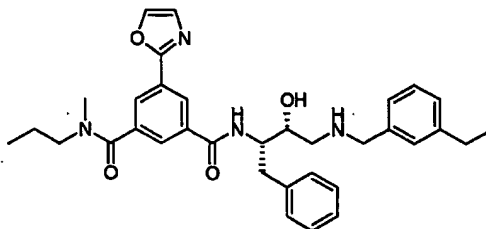
3-{[Methyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid



5 To a -70 °C stirred solution of oxazole (330 mg, 4.8 mmol) in tetrahydrofuran (4 mL) is added *n*-butyllithium (1.6 M in hexanes, 3.3 mL, 5.3 mmol). After 30 min, zinc chloride (1 M in diethyl ether, 14.5 mL, 14.5 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is  
10 added a solution of methyl 3-iodo-5-{[methyl(propyl)amino]carbonyl}benzoate (1.6 g, 4.5 mmol) in anhydrous tetrahydrofuran (3 mL) followed by palladium(0) tetrakis(triphenylphosphine) (221 mg, 0.19 mmol). The reaction mixture is heated at reflux for 2 h. The reaction  
15 mixture is cooled, diluted with ethyl acetate, washed with water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 60% ethyl acetate/hexane) provides a solid. The solid is redissolved in 1:1:1  
20 tetrahydrofuran/methanol/water (9 mL), and lithium hydroxide monohydrate (311 mg, 7.4 mmol) is added and stirred 2 h at room temperature. The reaction is diluted in chloroform and washed with 1N hydrochloric acid (aq), water, and brine, dried (sodium sulfate), filtered and concentrated under reduced  
25 pressure to give the title compound. ESI MS *m/z* 287.3 [M - H]<sup>-</sup>

## Step 3

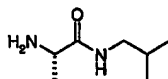
N<sup>1</sup>-{(1*S*,2*R*)-1-Benzyl-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-  
30 N<sup>3</sup>-methyl-5-(1,3-oxazol-2-yl)-N<sup>3</sup>-propylisophthalamide



To 3-{[methyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid (206 mg, 0.71 mmol) in DMF (5 mL) is added  
 5 diisopropylethylamine (174  $\mu$ L, 1.1 mmol), HATU (323 mg, 0.85 mmol), then (2R,3S)-3-amino-1-[(3-ethylbenzyl)amino]-4-phenylbutan-2-ol dihydrochloride prepared by the method of  
 EXAMPLE SP-272 (292 mg, 0.79 mmol). The reaction is stirred 4 h at room temperature. The reaction is partitioned between  
 10 chloroform and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) gives the title compound.  
 15 ESI MS  $m/z$  569.3  $[M + H]^+$ .

## EXAMPLE SP-164

## Step 1

 $N^1$ - Isobutyl-L-alaninamide

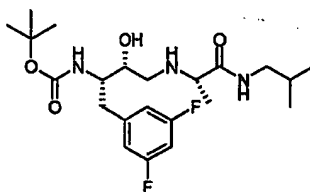
20 Boc-L-alanine (5.0 g, 26.4 mmol), isobutylamine (2.9 mL, 29.1 mmol), diisopropylethylamine (11.5 mL, 66 mmol), and HOBt (3.6 g, 26.4 mmol) in anhydrous DMF (15 mL) is stirred 15 min. EDC is added, and the reaction is stirred at room temperature  
 25 16 h. The reaction is diluted in ethyl acetate and washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. The residue is redissolved in 4N hydrochloric acid in dioxane (30 mL) and stirred for 2 h. The



solution is concentrated under reduced pressure, dissolved in chloroform and washed with 1 N NaOH (aq). The aqueous layer is extracted with chloroform, and the pooled organics are dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS  $m/z$  145.2  $[M + H]^+$ .

## Step 2

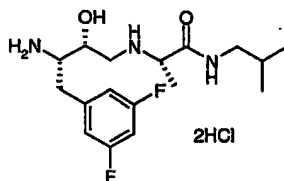
**[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1-isobutylcarbamoyl-ethylamino)-propyl]-carbamic acid tert-butyl ester**



$N^1$ - Isobutyl-L-alaninamide (3.8 g, 26 mmol) and tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate prepared by the method in EXAMPLE S-3 (3.1 g, 10.4 mmol) in isopropanol (50 mL) are refluxed 4 h. The reaction is cooled and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) gives the title compound. ESI MS  $m/z$  444.1  $[M + H]^+$ .

## Step 3

**$N^2$ -[(2R,3S)-3-Amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]- $N^1$ -isobutyl-L-alaninamide dihydrochloride**

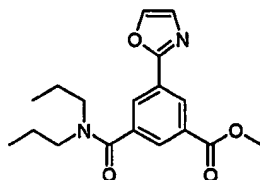


**[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1-isobutylcarbamoyl-ethylamino)-propyl]-carbamic acid tert-butyl ester** (2.7 g, 6 mmol) is dissolved in excess 4N hydrochloric acid in dioxane, and the reaction is stirred 2 h at room temperature. The solution is concentrated under reduced

pressure to give the title compound. ESI MS  $m/z$  344.3  $[M + H]^+$ .

#### Step 4

#### 5 Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoate

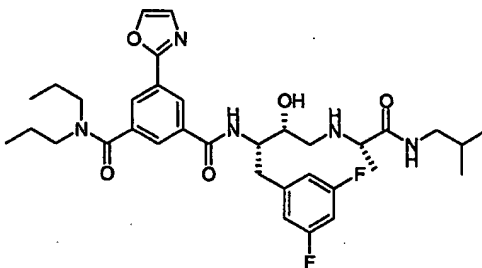


3-[(Dipropylamino)carbonyl]-5-iodobenzoic acid (12 g, 32 mmol) is dissolved in 20% methanol/benzene (480 mL), and 2M trimethylsilyldiazomethane in hexane (19 mL, 38 mmol) is added slowly. Upon completion of the addition, the solution is concentrated under reduced pressure to give methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate for use without further purification in the following reaction. To a -70 °C stirred solution of oxazole (120 mg, 1.7 mmol) in tetrahydrofuran (4 mL) is added *n*-butyllithium (1.6 M in hexanes, 1.2 mL, 1.9 mmol). After 30 min, zinc chloride (1 M in diethyl ether, 5.2 mL, 5.2 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is added a solution of methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (643 mg, 1.6 mmol) in anhydrous tetrahydrofuran (3 mL) followed by palladium(0) tetrakis(triphenylphosphine) (80 mg, 0.07 mmol). The reaction mixture is heated at reflux for 3 h. The reaction mixture is cooled, diluted with ethyl acetate, filtered, washed with saturated sodium bicarbonate, water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 60% ethyl acetate/hexane) provides the title compound in pure form.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.77 (s, 1H), 8.27 (s, 1H), 8.14 (s, 1H), 7.80 (s, 1H) 7.32 (s, 1H), 3.52 (t, 2H), 3.22 (t, 2H), 1.75 (m, 2H), 1.30 (m, 2H), 0.97 (t, 3H), 0.79 (t, 3H).

## Step 5

N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1-isobutylcarbamoyl-ethylamino)-propyl]-5-oxazol-2-yl-N',N'-dipropyl-

5 isophthalamide

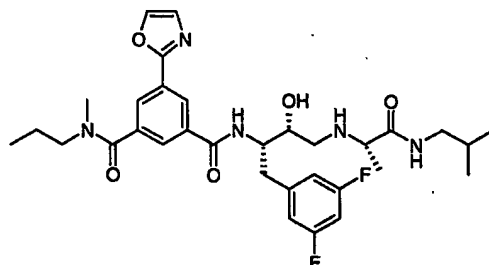


Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoate (430 mg, 1.3 mmol) is dissolved in 1:1:1 tetrahydrofuran/methanol/water (9 mL), and lithium hydroxide monohydrate (110 mg, 2.6 mmol) is added and stirred 2 h at room temperature. The reaction is concentrated under reduced pressure and chloroform is added. The solution is washed with 1N hydrochloric acid (aq). The aqueous layer is reextracted with chloroform, and the pooled organics are washed with brine. The solution is concentrated under reduced pressure.

To this residue redissolved in DMF (5 mL) is added diisopropylethylamine (438  $\mu$ L, 2.52 mmol), HATU (289 mg, 0.76 mmol), then N<sup>2</sup>-[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]-N<sup>1</sup>-isobutyl-L-alaninamide dihydrochloride (288 mg, 0.69 mmol). The reaction is stirred 4 h at room temperature. The reaction is partitioned between chloroform and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) gives the title compound. ESI MS  $m/z$  642.3 [M + H]<sup>+</sup>.

EXAMPLE SP-165

N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1-isobutylcarbamoyl-ethylamino)-propyl]-N'-methyl-5-oxazol-2-yl-N'-propyl-isophthalamide



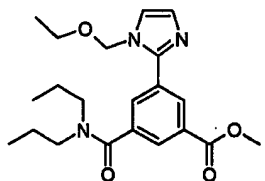
5           To           3-{[Methyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid prepared by the method in EXAMPLE SP-163 in DMF (5 mL) is added diisopropylethylamine (361  $\mu$ L, 2.1 mmol), HATU (237 mg, 0.62 mmol), then dihydrochloride prepared by the method of EXAMPLE SP-164 (237 mg, 0.57 mmol). The reaction is  
10 stirred 2 h at room temperature. The reaction is partitioned between chloroform and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column  
15 chromatography (silica, 8% methanol/chloroform) gives the title compound. ESI MS  $m/z$  614.4  $[M + H]^+$ .

#### EXAMPLE SP-166

N<sup>1</sup>-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[1-(ethoxymethyl)-1H-imidazol-2-yl]-N<sup>3</sup>,N<sup>3</sup>-dipropylisophthalamide

#### Step 1

Methyl           3-[(dipropylamino)carbonyl]-5-[1-(ethoxymethyl)-1H-imidazol-2-yl]benzoate

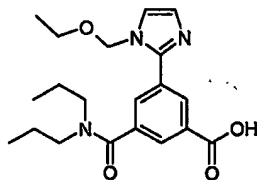


To a -70 °C stirred solution of 1-ethoxymethylimidazole (*J. Am. Chem. Soc.* **1978**, *100*, 3918) (420 mg, 3.3 mmol) in tetrahydrofuran (10 mL) is added *n*-butyllithium (1.6 M in hexanes, 2.3 mL, 3.6 mmol). After 30 min, zinc chloride (9.9 mL of a 1 M solution in diethyl ether, 9.9 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is then added methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (1.17 g, 3 mmol) followed by palladium(0) tetrakis(triphenylphosphine) (173 mg, 0.15 mmol). The reaction mixture is heated at reflux for 2 h. The reaction mixture is diluted with ethyl acetate (50 mL), washed with water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 1-5% methanol/methylene chloride) provides the title compound in pure form. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.52 (s, 1H), 8.10 (s, 1H), 8.03 (s, 1H), 8.19 (s, 2H), 5.28 (s, 2H), 3.95 (s, 3H), 3.59 (q, *J* = 7 Hz, 2H), 3.49 (m, 2H), 3.21 (m, 2H), 1.70 (m, 2H), 1.54 (m, 2H), 1.25 (t, *J* = 7 Hz, 3H), 0.99 (m, 3H), 0.75 (m, 3H).

20

## Step 2

3-[(Dipropylamino)carbonyl]-5-[1-(ethoxymethyl)-1H-imidazol-2-yl]benzoic acid



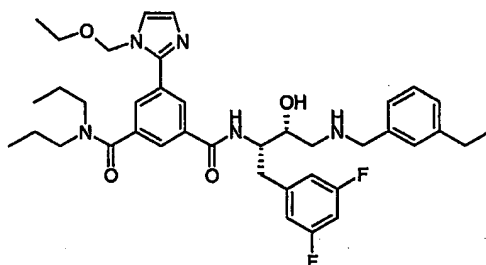
To a stirred solution of the ester from step 1 (756 mg, 1.95 mmol) in 2:1:1 tetrahydrofuran/methanol/water (12 mL) is added lithium hydroxide (170 mg, 4 mmol). The reaction mixture is stirred at room temperature for 42 h, and concentrated under reduced pressure. The residue is partitioned between water (10 mL) and chloroform (10 mL). The aqueous layer is acidified to pH 4 - 5 with 1 N hydrochloric

30

acid and extracted with 3:1 chloroform/2-propanol (3 x 30 mL). The combined organic layers are dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide the title compound. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 8.51 (s, 1H), 8.06 (s, 1H), 8.00 (s, 1H), 7.49 (s, 1H), 7.17 (s, 1H), 5.39 (s, 2H), 3.62 (q, *J* = 7 Hz, 2H), 3.51 (m, 2H), 3.27 (m, 2H), 1.72 (m, 2H), 1.59 (m, 2H), 1.21 (t, *J* = 7 Hz, 3H), 1.00 (m, 3H), 0.75 (m, 3H).

### 10 Step 3

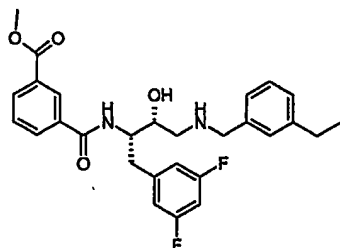
N<sup>1</sup>-{(1*S*, 2*R*)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[1-(ethoxymethyl)-1*H*-imidazol-2-yl]-N<sup>3</sup>, N<sup>3</sup>-dipropylisophthalamide



15 To a stirred solution of 3-[(dipropylamino)carbonyl]-5-[1-(ethoxymethyl)-1*H*-imidazol-2-yl]benzoic acid (177 mg, 0.47 mmol), diisopropylethylamine (651 mg, 0.5 mmol), and HBTU (209 mg, 0.55 mmol) in methylene chloride (5 mL) is added a mixture of (2*R*, 3*S*)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (196 mg, 0.48 mmol) and diisopropylethylamine (130 mg, 1.0 mmol) in methylene chloride (5 mL). The reaction mixture is stirred at room temperature for 15 h and concentrated under reduced pressure. The residue is diluted with ethyl acetate (20 mL), washed with saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5:95 methanol/methylene chloride) provides the title compound. APCI MS *m/z* 690.3 [*M* + *H*]<sup>+</sup>.

## EXAMPLE SP-168

Methyl 3-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]benzoate



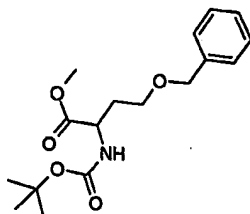
5

To methyl hydrogen isophthalate (1.0 g, 5.6 mmol) in DMF/chloroform (1:2, 15 mL) is added diisopropylethylamine (3.9 mL, 22 mmol), HATU (2.5 g, 6.7 mmol), then (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (2.5 g, 6.1 mmol). The reaction is stirred 1 h at room temperature. The reaction is partitioned between ethyl acetate and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) gives the title compound. ESI MS  $m/z$  497.3  $[M + H]^+$ .

20 EXAMPLE SP-169 N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[4-(2-hydroxyethyl)-1,3-oxazol-2-yl]benzamide

## Step 1

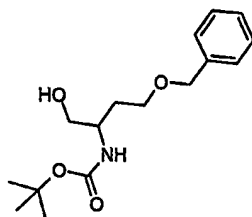
25 Methyl O-benzyl-N-(tert-butoxycarbonyl)homoserinate



To O-benzyl-N-(tert-butoxycarbonyl)homoserine (5.8 g, 18.9 mmol) in 20% methanol/benzene (72 mL) is added 2M trimethylsilyldiazomethane in hexane (12.3 mL, 24.5 mmol), and the reaction stirred at room temperature 1.5 h. The solution  
5 is concentrated under reduced pressure to give the title compound in pure form. ESI MS  $m/z$  324.2  $[M + H]^+$ .

## Step 2

tert-Butyl 3-(benzyloxy)-1-(hydroxymethyl)propylcarbamate

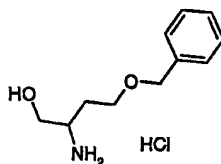


10

To an ice-cold solution of methyl O-benzyl-N-(tert-butoxycarbonyl)homoserinate (6 g, 18.6 mmol) in absolute ethanol (100 mL) is added sodium borohydride (2.8 g, 74.2 mmol), and the reaction is refluxed 2 h. The solution is  
15 cooled, excess saturated potassium carbonate added, and stirred 16 h at room temperature. The ethanol is removed under reduced pressure, and the aqueous solution is extracted with chloroform. The organic layer is washed with saturated sodium bicarbonate, saturated sodium sulfate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to  
20 give the title compound. ESI MS  $m/z$  296.2  $[M + H]^+$ .

## Step 3

2-Amino-4-(benzyloxy)butan-1-ol hydrochloride



25

tert-Butyl 3-(benzyloxy)-1-(hydroxymethyl)propylcarbamate (5 g, 17 mmol) is dissolved in 4 N hydrochloric acid in



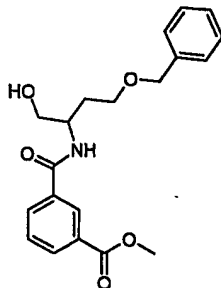
dioxane (21 mL) and stirred for 3 h at room temperature. The solution is concentrated under reduced pressure to give the title compound in pure form. ESI MS  $m/z$  196.1  $[M + H]^+$ .

5 Step 4

Methyl

3-([3-(benzyloxy)-1-

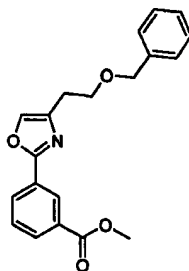
(hydroxymethyl)propyl]amino)carbonyl)benzoate



Methyl hydrogen isophthalate (1.5 g, 8.2 mmol), 2-amino-  
 10 4-(benzyloxy)butan-1-ol hydrochloride (2 g, 8.6 mmol),  
 diisopropylethylamine (4.2 mL, 24.7 mmol), and HATU (3.8 mg,  
 9.9 mmol), in DMF (15 mL) are stirred at room temperature 1 h.  
 The reaction is diluted in ethyl acetate and washed with  
 water, 1N hydrochloric acid (aq), saturated sodium  
 15 bicarbonate, brine, dried (magnesium sulfate), filtered, and  
 concentrated under reduced pressure. Purification by flash  
 column chromatography (silica gel, 4% methanol/chloroform)  
 provides the title compound.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.44  
 (s, 1H), 8.18 (d, 1H,  $J = 7.9$  Hz), 7.86 (d, 1H,  $J = 7.9$  Hz),  
 20 7.43 (t, 1H,  $J = 7.6$  Hz), 7.42-7.35 (m, 5 H), 4.59 (s, 2H),  
 4.33 (m, 1H), 3.96 (s, 3H), 3.88-3.72 (m, 4H), 3.53 (s, 1H),  
 2.08 (m, 2H).

Step 5

25 Methyl 3-{4-[2-(benzyloxy)ethyl]-1,3-oxazol-2-yl}benzoate

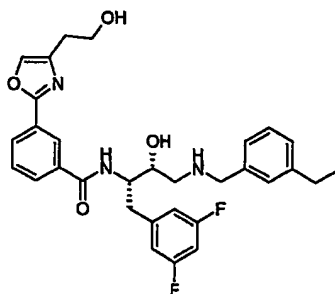


To methyl 3-([3-(benzyloxy)-1-(hydroxymethyl)propyl]amino)benzoate (1.3 g, 3.6 mmol) in water-saturated methylene chloride (20 mL) is added sodium bromide (187 mg, 1.8 mmol) and water (2.75 mL), then TEMPO (6 mg, 0.04 mmol) with vigorous stirring. Sodium bicarbonate (115 mg) and 6% sodium hypochlorite (5 mL) is added and stirred 1 h. 6% sodium hypochlorite (1 mL) is added each hour for 3 h.

Excess saturated sodium thiosulfate is added and stirred 30 min. The mixture is partitioned, and the organic layer is washed with brine, dried (sodium sulfate), filtered and concentrated under reduced. The residue is dissolved in anhydrous tetrahydrofuran (4 mL), and (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt (670 mg, 2.8 mmol). The reaction is microwaved (100 W, 2 min) in a sealed vessel, cooled, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 40% ethyl acetate/hexanes) gives the title compound. ESI MS  $m/z$  338.3  $[M + H]^+$ .

#### Step 6

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[4-(2-hydroxyethyl)-1,3-oxazol-2-yl]benzamide



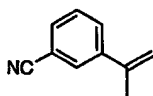
Methyl 3-{4-[2-(benzyloxy)ethyl]-1,3-oxazol-2-yl}benzoate  
 (300 mg, 0.9 mmol), 20% palladium(II) hydroxide on carbon (65  
 mg), and cyclohexene (3 mL) in absolute ethanol (3 mL) are  
 5 refluxed 1 h. The reaction is cooled, filtered through  
 diatomaceous earth, and concentrated under reduced pressure.  
 The residue is redissolved in 2:1:1  
 tetrahydrofuran/methanol/water (4 mL) is added lithium  
 hydroxide (75 mg, 1.8 mmol). The reaction mixture is stirred  
 10 at room temperature for 3 h, and concentrated under reduced  
 pressure. The residue is dissolved in DMF (5 mL), and  
 diisopropylethylamine (625  $\mu$ L, 3.6 mmol), HATU (540 mg, 1.4  
 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-  
 ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the  
 15 method in EXAMPLE SP-272 (407 mg, 1 mmol) are added. The  
 reaction stirred at room temperature 16 h. The reaction  
 mixture is diluted with chloroform, washed with water, 1N  
 hydrochloric acid (aq), saturated sodium bicarbonate, brine,  
 dried (sodium sulfate), filtered, and concentrated under  
 20 reduced pressure. Purification by flash column chromatography  
 (silica, 8% methanol/chloroform) provides the title compound.  
 ESI MS  $m/z$  550.3  $[M + H]^+$ .

#### EXAMPLE SP-170

25  $N^1$ -{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-  
 isopropylbenzyl)amino]propyl}- $N^3,N^3$ -dipropyl-5-(1,3-thiazol-2-  
 yl)isophthalamide

#### Step 1

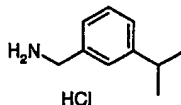
## 3-Isopropenylbenzonitrile



To a stirred solution of 3-cyanophenylboronic acid (10.0 g, 68.05 mmol) dissolved in DME (340 mL) is added 2-bromopropene (6.86 g, 56.7 mmol), and sodium carbonate (62.3 mL of a 2 M solution in water, 124.7 mmol). The reaction mixture is degassed for 20 min with nitrogen. Tetrakis(triphenylphosphine)palladium(0) (2.54 g, 2.2 mmol) is added, the reaction mixture degassed for 10 min, and heated at reflux overnight. The reaction mixture is cooled to room temperature and then partitioned between hexanes and water. The aqueous layer is extracted with hexanes (3 x 75 mL). The combined organic layers are washed with brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (9:1 hexanes/ethyl acetate) provides the title compound. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 7.96 (m, 1H), 7.85 (d, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 1H), 7.56 (m, 1H) 5.58 (s, 1H), 5.23 (m, 1H), 2.13 (s, 3H).

## Step 2

## 3-Isopropylbenzylamine hydrochloride

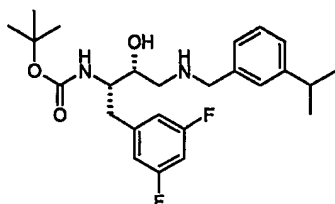


A solution of 3-isopropenylbenzonitrile (6.0 g, 41.9 mmol) and 10% Pd/C (600 mg) in ethanol (65 mL) and acetic acid (2.4 mL) is degassed with nitrogen for 15 min, and shaken under an atmosphere of hydrogen at 50 psi for 12 h. The reaction mixture is filtered through diatomaceous earth and concentrated under reduced pressure to provide an oil. The oil is dissolved in methanol (5 mL) and hydrochloric acid (15 mL of a 1 M solution in diethyl ether) is added. The

resulting precipitate is collected by filtration to provide the title compound. APCI MS  $m/z$  149  $[M + H]^+$ .

### Step 3

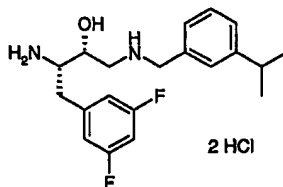
- 5 tert-Butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propylcarbamate



- tert-Butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (2.0 g, 6.7 mmol) and 3-isopropylbenzylamine  
 10 hydrochloride (2.5 g, 13.5 mmol) in isopropanol (60 mL) are refluxed 3 h. The reaction is cooled and stirred 16 h. The solution is concentrated under reduced pressure, redissolved in chloroform, washed with 1N hydrochloric acid, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered  
 15 and concentrated under reduced pressure. Purification by flash chromatography (silica, 7% methanol/chloroform) gives the title compound in pure form. ESI MS  $m/z$  449.3  $[M + H]^+$ .

### Step 4

- 20 (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-isopropylbenzyl)amino]butan-2-ol dihydrochloride

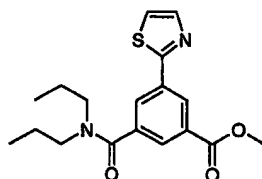


- tert-Butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propylcarbamate (1.5 g, 3.3 mmol) is  
 25 dissolved in 4 N hydrochloric acid in dioxane (20 mL), and the reaction is stirred at room temperature 3 h. The mixture is

concentrated under reduced pressure to afford the title compound. ESI MS  $m/z$  349.2  $[M + H]^+$ .

Step 5

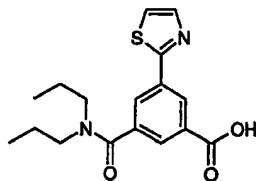
- 5 Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate



- To 0.5 M thiazole zinc bromide in tetrahydrofuran (45 mL) is added methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate  
10 (8.6 g, 21.4 mmol) in anhydrous tetrahydrofuran (130 mL) followed by palladium(0) tetrakis(triphenylphosphine) (2 g, 1.7 mmol). The reaction mixture is heated at reflux for 16 h. The reaction mixture is diluted with ethyl acetate (50 mL), washed with water, saturated sodium bicarbonate, and brine,  
15 dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 35% ethyl acetate/hexanes) provides the title compound. ESI MS  $m/z$  347.1  $[M + H]^+$ .

20 Step 6

- 3-[(Dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid

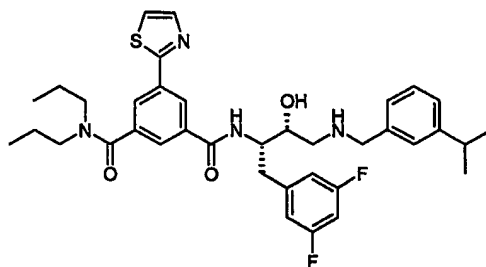


- Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate (4.4 g, 12.8 mmol) is dissolved in 1:1:1  
25 tetrahydrofuran/methanol/water (60 mL), and lithium hydroxide monohydrate is added (1.1 g, 25.6 mmol). The reaction is stirred 15 min and is concentrated under reduced pressure. The residue is diluted in chloroform and washed with water,

brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS  $m/z$  333.1  $[M + H]^+$ .

5 Step 7

$N^1$ -(1*S*,2*R*)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}- $N^3,N^3$ -dipropyl-5-(1,3-thiazol-2-yl)isophthalamide



10

3-[(Dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid is dissolved in DMF (8 mL), and diisopropylethylamine (456  $\mu$ L, 2.6 mmol), HATU (342 mg, 0.9 mmol), and (2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-[(3-

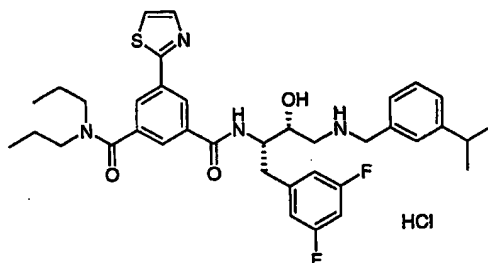
15 isopropylbenzyl)amino]butan-2-ol dihydrochloride (350 mg, 0.83 mmol) are added. The reaction stirred at room temperature 1 h. The reaction is partitioned between ethyl acetate and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (5 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS  $m/z$  663.3  $[M + H]^+$ .

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EXAMPLE SP-171

$N^1$ -{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}- $N^3,N^3$ -dipropyl-5-(1,3-thiazol-2-yl)isophthalamide hydrochloride



5

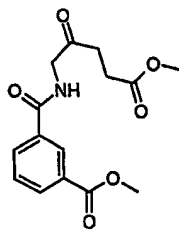
$N^1$ -{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}- $N^3,N^3$ -dipropyl-5-(1,3-thiazol-2-yl)isophthalamide (180 mg, 0.27 mmol) is dissolved in diethyl ether (5 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS  $m/z$  663.3  $[M + H]^+$ .

#### EXAMPLE SP-172

Methyl 3-(2-{3-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]phenyl)-1,3-oxazol-5-yl)propanoate

#### Step 1

Methyl 3-[(5-methoxy-2,5-dioxopentyl)amino]carbonyl)benzoate



20

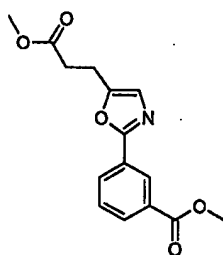
Methyl hydrogen isophthalate (1.8 g, 10.2 mmol) is dissolved in methylene chloride (10 mL) and DMF (10 mL), and diisopropylethylamine (4.4 mL, 25.5 mmol), HATU (4.6 g, 12.2 mmol), and 5-aminolevulinic acid methyl ester hydrochloride (2 g, 11.2 mmol) are added. The reaction stirred at room



temperature 1 h. The reaction is partitioned between ethyl acetate and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provides the title compound. ESI MS  $m/z$  306.1  $[M - H]^-$ .

## Step 2

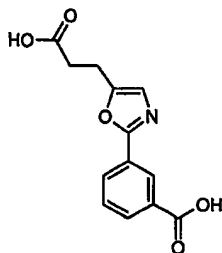
10 Methyl 3-[5-(3-methoxy-3-oxopropyl)-1,3-oxazol-2-yl]benzoate



Methyl 3-[[5-methoxy-2,5-dioxopentyl)amino]carbonyl]benzoate (520 mg, 1.7 mmol) is dissolved in anhydrous tetrahydrofuran (4 mL), and (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt (810 mg, 3.4 mmol). The reaction is microwaved (100 W, 2 min) in a sealed vessel, cooled, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 40% ethyl acetate/hexanes) gives the title compound. ESI MS  $m/z$  290.1  $[M + H]^+$ .

## Step 3

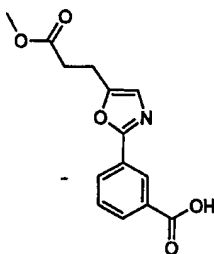
3-[5-(2-Carboxyethyl)-1,3-oxazol-2-yl]benzoic acid



To methyl 3-[5-(3-methoxy-3-oxopropyl)-1,3-oxazol-2-yl]benzoate (400 mg, 1.3 mmol) in 2:1:1 tetrahydrofuran/methanol/water (8 mL) is added lithium hydroxide monohydrate (112 mg, 2.7 mmol), and the reaction is stirred 2 h at room temperature. More lithium hydroxide monohydrate (225 mg, 5.4 mmol) is added and the reaction is stirred 16 h at room temperature. The reaction is treated with excess concentrated hydrochloric acid resulting in a precipitate. The precipitate is filtered to give the title compound. ESI MS  $m/z$  260.1  $[M - H]^-$ .

## Step 4

3-[5-(3-Methoxy-3-oxopropyl)-1,3-oxazol-2-yl]benzoic acid

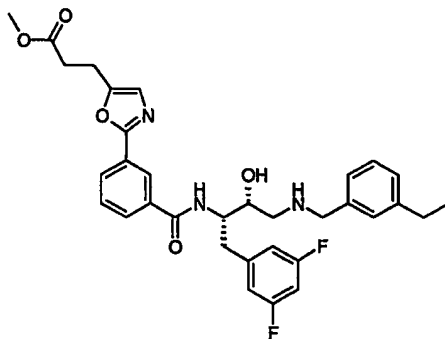


15

To 3-[5-(2-carboxyethyl)-1,3-oxazol-2-yl]benzoic acid (317 mg, 1.2 mmol) in methanol (5 mL) is added thionyl chloride (4.4  $\mu$ L, 0.06 mmol), and the reaction is stirred at room temperature 16 h. The solution is concentrated under reduced pressure to give the title compound. ESI MS  $m/z$  274.1  $[M - H]^-$ .

## Step 5

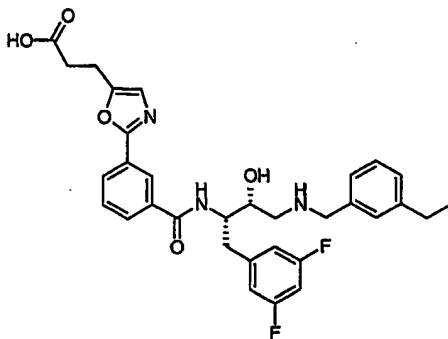
Methyl 3-(2-{3-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]phenyl}-1,3-oxazol-5-yl)propanoate



3-[5-(3-Methoxy-3-oxopropyl)-1,3-oxazol-2-yl]benzoic acid (285 mg, 1.0 mmol) is dissolved in methylene chloride (5 mL) and DMF (5 mL), and diisopropylethylamine (695  $\mu$ L, 4.0 mmol),  
 5 HATU (472 g, 1.2 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (448 mg, 1.1 mmol) are added. The reaction stirred at room temperature 1 h. The reaction is partitioned between ethyl  
 10 acetate and saturated sodium bicarbonate. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform)  
 15 provides the title compound. ESI MS  $m/z$  591.9  $[M + H]^+$ .

## EXAMPLE SP-173

3-(2-{3-[(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino}carbonyl]phenyl)-1,3-oxazol-5-yl)propanoic acid  
 20



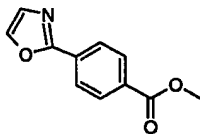
Methyl 3-(2-{3-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]phenyl}-1,3-oxazol-5-yl)propanoate (70 mg, 0.12 mmol) and lithium hydroxide monohydrate (10 mg, 0.24 mmol) in 2:1:1  
 5 tetrahydrofuran/methanol/water (6 mL) is stirred at room temperature 1.5 h. The reaction is concentrated under reduced pressure. The residue is washed with 1N hydrochloric acid (aq), then chloroform, and the solid is dried under reduced pressure to give the title compound. ESI MS  $m/z$  578.2 [M +  
 10 H]<sup>+</sup>.

## EXAMPLE SP-174

N-[(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-  
 15 hydroxypropyl]-4-(1,3-oxazol-2-yl)benzamide

## Step 1

Methyl 4-(1,3-oxazol-2-yl)benzoate

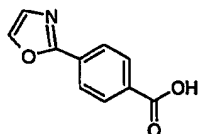


20 To a -70 °C, stirred solution of oxazole (190  $\mu$ L, 3.8 mmol) in tetrahydrofuran (10 mL) is added *n*-butyl lithium (2.6 mL of a 1.6 M solution in hexanes, 4.2 mmol). After 30 min, zinc chloride (11.5 mL of a 1.0 M solution in diethyl ether, 11.5 mmol) is added. The reaction mixture is warmed to 0 °C  
 25 and methyl 4-iodobenzoate (1 g, 3.8 mmol) and palladium(0) tetrakis(triphenylphosphine) (530 mg, 0.4 mmol) are added. The reaction mixture is heated at 70 °C for 20 h under argon, cooled to room temperature, and then partitioned between ethyl acetate and water. The organic layer is washed with water and  
 30 brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (3:1 hexanes/ethyl acetate) yields the title

compound.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14 (s, 4H), 8.07–8.05 (m, 1H), 7.36–7.35 (m, 1H), 3.95 (s, 3H).

## Step 2

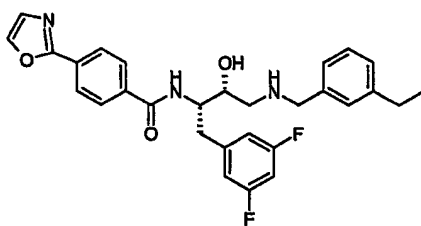
### 5 4-(1,3-Oxazol-2-yl)benzoic acid



To a stirred solution of methyl 4-(1,3-oxazol-2-yl)benzoate (690 mg, 3.4 mmol) in a mixture of 2:1:1 tetrahydrofuran/methanol/water (20 mL) is added lithium hydroxide (430 mg, 3 mmol). The reaction mixture is stirred at room temperature for 2 h. The solvent is removed under reduced pressure and the residue is partitioned between diethyl ether and water. The aqueous layer is acidified to pH 1 with 1 N hydrochloric acid and a precipitate is observed. The solid is collected by filtration to afford the title compound.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.14 (s, 4H), 8.05 (s, 1H), 7.36 (s, 1H).

## Step 3

### 20 N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(1,3-oxazol-2-yl)benzamide



To a solution of 4-(1,3-oxazol-2-yl)benzoic acid (105 mg, 0.6 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (220 mg, 0.6 mmol), and HATU (210 mg, 0.6 mmol) stirring in methylene chloride (5 mL) is added *N,N*-diisopropylethylamine (340  $\mu\text{L}$ , 1.9 mmol). The reaction mixture is stirred at room

temperature for 18 h. The reaction mixture is partitioned between methylene chloride and water. The organic layer is washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude solid.

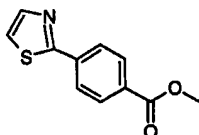
- 5 Purification by flash column chromatography (silica, gradient 96:4 to 93:7 methylene chloride/methanol) provided the title compound. ESI MS  $m/z$  506.2  $[M + H]^+$ .

#### EXAMPLE SP-173

- 10 N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(1,3-thiazol-2-yl)benzamide

##### Step 1

Methyl 4-(1,3-thiazol-2-yl)benzoate

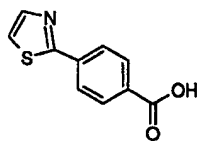


15

- To a -70 °C, stirred solution of thiazole (270  $\mu$ L, 3.8 mmol) in tetrahydrofuran (10 mL) is added *n*-butyl lithium (2.6 mL of a 1.6 M solution in hexanes, 4.2 mmol). After 30 min, zinc chloride (11.4 mL of a 1.0 M solution in diethyl ether, 11.4 mmol) is added. The reaction mixture is warmed to 0 °C and methyl 4-iodobenzoate (1 g, 3.8 mmol) and palladium(0) tetrakis(triphenylphosphine) (530 mg, 0.4 mmol) are added. The reaction mixture is heated at 70 °C for 20 h under argon, cooled to room temperature, and then partitioned between ethyl acetate and water. The organic layer is washed with water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (3:1 hexanes/ethyl acetate) yields the title compound.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14-8.03 (m, 4H), 7.93-7.92 (m, 1H), 7.42-7.41 (m, 1H), 3.95 (s, 3H).
- 20  
25  
30

##### Step 2

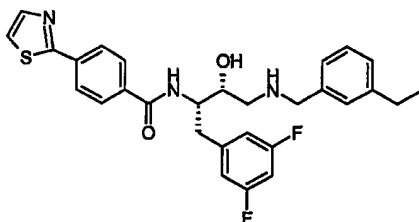
## 4-(1,3-Thiazol-2-yl)benzoic acid



To a stirred solution of methyl 4-(1,3-thiazol-2-yl)benzoate (560 mg, 2.6 mmol) in a mixture of 2:1:1  
5 tetrahydrofuran/methanol/water (20 mL) is added lithium hydroxide (322 mg, 3 mmol). The reaction mixture is stirred at room temperature for 2 h. The solvent is removed under reduced pressure and the residue is partitioned between diethyl ether and water. The aqueous layer is acidified to pH  
10 1 with 1 N hydrochloric acid and a precipitate is observed. The solid is collected by filtration to afford the title compound. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 8.14-8.05 (m, 4H), 7.95-7.93 (m, 1H), 7.71-7.69 (m, 1H).

## 15 Step 3

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-(1,3-thiazol-2-yl)benzamide

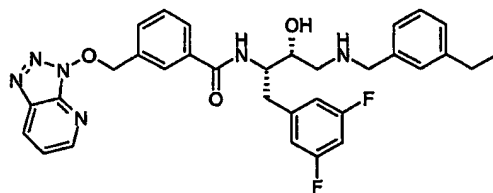


To a solution of 4-(1,3-thiazol-2-yl)benzoic acid (110  
20 mg, 0.6 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (220 mg, 0.6 mmol), and HATU (210 mg, 0.6 mmol) stirring in methylene chloride (5 mL) is added *N,N*-diisopropylethylamine (340 μL, 1.9 mmol). The reaction mixture is stirred at room  
25 temperature for 18 h. The reaction mixture is partitioned between methylene chloride and water. The organic layer is washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash

column chromatography (silica, gradient 95:5 to 92:8 methylene chloride/methanol) provides the title compound. ESI MS  $m/z$  522.2  $[M + H]^+$ .

5 EXAMPLE SP-176

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methyl]benzamide



10 To 3-(bromomethyl)benzoic acid (200 mg, 0.93 mmol) and diisopropylethylamine (566  $\mu$ L, 3.26 mmol) in DMF (5 mL) is added HATU (424 mg, 1.12 mmol), and the reaction is stirred 5 min. To the reaction is added (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol

15 dihydrochloride prepared by the method in EXAMPLE SP-272 (379 mg, 0.93 mmol), and the reaction stirred 30 min. The reaction mixture is diluted with methylene chloride, washed with 1 N hydrochloric acid (15 mL), saturated sodium bicarbonate (15 mL), and brine. The organic layer is then dried (sodium

20 sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) provides the title compound. ESI MS  $m/z$  587.4  $[M + H]^+$ .

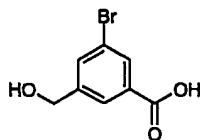
25 EXAMPLE SP-177

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-[(2-hydroxyethyl)(propyl)amino]methyl}-5-methylbenzamide dihydrochloride

30 Step 1



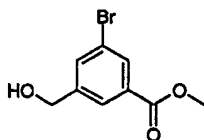
## 3-Bromo-5-(hydroxymethyl)benzoic acid



To an ice-cold solution of 3-bromo-5-(methoxycarbonyl)benzoic acid prepared by the method in Preparation 2 (10.3 g, 40 mmol) in anhydrous tetrahydrofuran (100 mL) is added lithium borohydride (12 g, 550 mmol) portion-wise. The reaction is stirred 4 h at this temperature. Absolute ethanol (20 mL) is added dropwise, and the reaction is stirred 1.5 h. The reaction is slowly poured on ice, and 10 % hydrochloric acid (aq) is added until gas evolution ceased. The aqueous layer is extracted with chloroform, and the organic layer is washed with brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS  $m/z$  229, 231  $[M - H]^-$ .

## Step 2

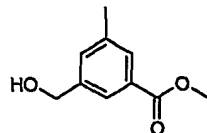
## Methyl 3-bromo-5-(hydroxymethyl)benzoate



To 3-bromo-5-(hydroxymethyl)benzoic acid (7.0 g, 30 mmol) in 20% methanol/benzene (100 mL) is added trimethylsilyldiazomethane (2M in hexanes), and the reaction is stirred 16 h. The reaction is concentrated under reduced pressure to afford the title compound. ESI MS  $m/z$  244.0  $[M + H]^+$ .

## Step 3

## Methyl 3-(hydroxymethyl)-5-methylbenzoate



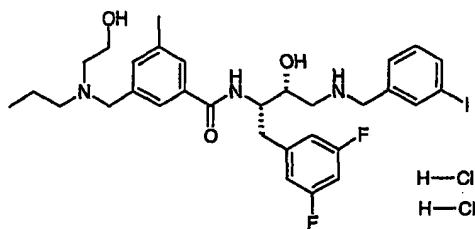
To a stirred solution of methyl 3-bromo-5-(hydroxymethyl)benzoate (3.0 g, 12.2 mmol) in dioxane (27 mL) is added cesium carbonate (4.0 g, 12.2 mmol), potassium carbonate (34 g, 24.4 mmol), and palladium(0) tetrakis(triphenylphosphine) (704 mg, 0.61 mmol), followed by trimethyl boroxine (1.7 mL, 12.2 mmol). The reaction mixture is refluxed for 5 h, cooled to room temperature, and then partitioned between water and ethyl acetate. The organic layer is washed with water, saturated sodium bicarbonate, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 20% ethyl acetate/hexanes) provides the title compound. ESI MS  $m/z$  181.2  $[M + H]^+$ .

15

## Step 4

N-((1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-3-[[2-hydroxyethyl](propyl)amino]methyl]-5-methylbenzamide dihydrochloride

20



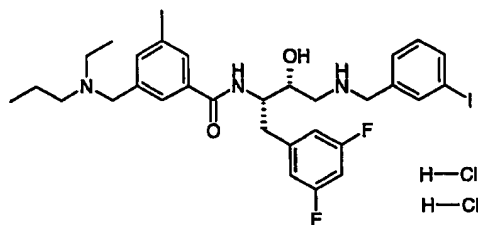
To a stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (1.25, 7 mmol) in methylene chloride (30 mL) at -30 °C is added methanesulfonyl chloride (752  $\mu$ L, 9.7 mmol) followed by triethylamine (1.95 mL, 14 mmol). The reaction mixture is stirred for 15 min at 0 °C. The reaction is diluted in diethyl ether and washed with water and cold brine, dried (magnesium sulfate), filtered and concentrated under reduced

pressure to give an oil. The residue is redissolved in anhydrous methylene chloride (22 mL). From this stock solution, 2 mL is added to a solution of N-hydroxyethylpropylamine (115  $\mu$ L, 1 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure.

Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 1:1:1 tetrahydrofuran/methanol/water (3 mL), and lithium hydroxide monohydrate is added (33 mg, 0.75 mmol). The reaction is stirred 2 h and is concentrated under reduced pressure. The residue is redissolved in DMF (3 mL), and diisopropylethylamine (261  $\mu$ L, 1.5 mmol), HATU (214 mg, 0.56 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (189 mg, 0.37 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 8% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS  $m/z$  666.2  $[M + H]^+$ .

#### EXAMPLE SP-178

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-{[ethyl(propyl)amino]methyl}-5-methylbenzamide dihydrochloride



Analogous to the method described in EXAMPLE SP-177, Step 4, 2 mL of the stock solution is added to a solution of *N*-ethylpropylamine (143  $\mu$ L, 1 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure.

10 Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 1:1:1 tetrahydrofuran/methanol/water (3 mL), and lithium hydroxide monohydrate is added (42 mg, 1 mmol). The reaction is stirred 2 h and is concentrated under reduced pressure.

15 The residue is redissolved in DMF (5 mL), and diisopropylethylamine (265  $\mu$ L, 1.5 mmol), (2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (252 mg, 0.5 mmol), and HATU (237 mg, 0.62 mmol) are added. The reaction stirred at room temperature

20 h. Purification by flash column chromatography (silica, 10% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the

25 title compound. ESI MS  $m/z$  650.2  $[M + H]^+$ .

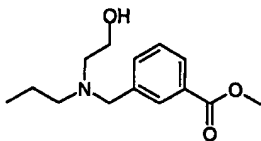
## EXAMPLE SP-179

*N*-{(1*S*,2*R*)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-[(2-hydroxyethyl)(propyl)amino]methoxybenzamide dihydrochloride

30

## Step 1

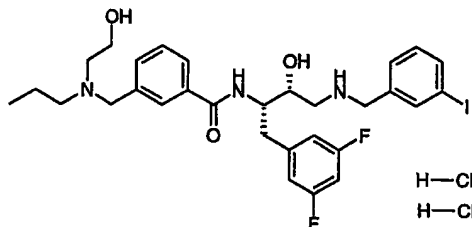
Methyl 3-[[ (2-hydroxyethyl) (propyl) amino] methyl] benzoate



To 2-propylaminomethanol (505  $\mu$ L, 4.4 mmol) in chloroform  
 5 (20 mL) is added methyl bromomethylbenzoate (1 g, 4.4 mmol),  
 and the reaction stirred at room temperature 16 h. The  
 reaction is washed with saturated sodium bicarbonate and  
 brine. The organic layer is then dried (sodium sulfate),  
 filtered, and concentrated under reduced pressure.  
 10 Purification by flash column chromatography (silica, 80% ethyl  
 acetate/hexanes) provides the title compound. ESI MS  $m/z$   
 252.3  $[M + H]^+$ .

## Step 2

15 N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-  
 iodobenzyl) amino] propyl}-3-[[ (2-  
 hydroxyethyl) (propyl) amino] methyl] benzamide dihydrochloride

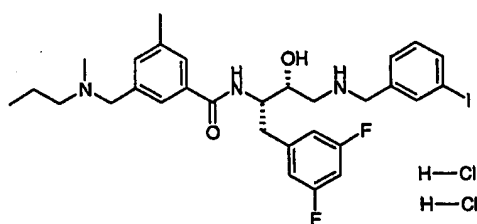


Methyl 3-[[ (2-hydroxyethyl) (propyl) amino] methyl] benzoate  
 20 (500 mg, 2 mmol) and lithium hydroxide monohydrate (170 mg, 4  
 mmol) are stirred in 2:1:1 tetrahydrofuran/methanol/water (4  
 mL) at room temperature for 16 h. The reaction is  
 concentrated under reduced pressure and redissolved in DMF (15  
 mL). To this solution is added (2R,3S)-3-amino-4-(3,5-  
 25 difluorophenyl)-1-[(3-iodobenzyl) amino] butan-2-ol  
 dihydrochloride (1 g, 2 mmol), diisopropylethylamine (1.4 mL,  
 8 mmol), then HATU (1.1 g, 3 mmol), and the reaction stirred 2  
 h. Purification by flash column chromatography (silica, 10%

methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (5 mL) and 1N hydrochloric acid in diethyl ether (3 mL) is added. The mixture is concentrated under reduced pressure to yield the  
 5 title compound. ESI MS  $m/z$  652.2  $[M + H]^+$ .

## EXAMPLE SP-180

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-methyl-5-  
 10 {[(methyl(propyl)amino)methyl]benzamide dihydrochloride

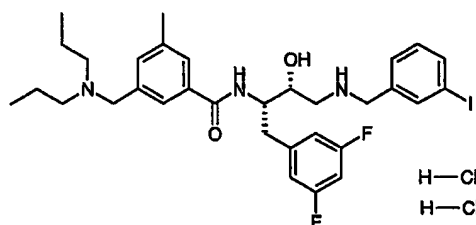


Analogous to the method described in EXAMPLE SP-177, Step 4, 2 mL of the stock solution is added to a solution of N-methylpropylamine (103  $\mu$ L, 1 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room  
 15 temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure.  
 20 Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 1:1:1 tetrahydrofuran/methanol/water (3 mL), and lithium hydroxide monohydrate is added (33 mg, 0.75 mmol). The reaction is stirred 2 h and is concentrated under reduced  
 25 pressure. The residue is redissolved in DMF (3 mL), and diisopropylethylamine (261  $\mu$ L, 1.5 mmol), HATU (214 mg, 0.56 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (189 mg, 0.37 mmol) are added. The reaction stirred at room temperature 16  
 30 h. Purification by flash column chromatography (silica, 8%

methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the  
5 title compound. ESI-MS  $m/z$  636.2  $[M + H]^+$ .

## EXAMPLE SP-181

N-((1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-3-[(dipropylamino)methyl]-5-  
10 methylbenzamide dihydrochloride

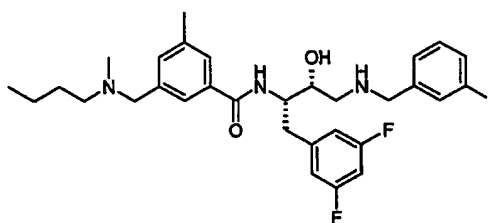


Analogous to the method described in EXAMPLE SP-177, Step 4, 2 mL of the stock solution is added to a solution of dipropylamine (137  $\mu$ L, 1 mmol) in anhydrous methylene chloride  
15 (1 mL), and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure.  
20 Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 1:1:1 tetrahydrofuran/methanol/water (3 mL), and lithium hydroxide monohydrate is added (33 mg, 0.75 mmol). The reaction is stirred 2 h and is concentrated under reduced  
25 pressure. The residue is redissolved in DMF (3 mL), and diisopropylethylamine (261  $\mu$ L, 1.5 mmol), HATU (214 mg, 0.56 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (189 mg, 0.37 mmol) are added. The reaction stirred at room temperature 16  
30 h. Purification by flash column chromatography (silica, 8%

methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the  
5 title compound. ESI MS  $m/z$  664.2  $[M + H]^+$ .

## EXAMPLE SP-182

3-{[Butyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-  
difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-5-  
10 methylbenzamide dihydrochloride



2 HCl

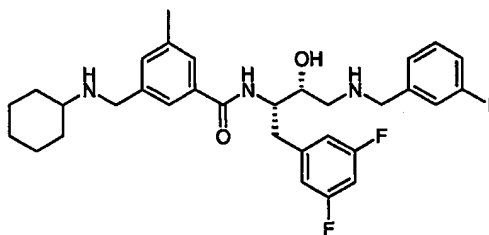
Analogous to the method described in EXAMPLE SP-177 Step 4, 2 mL of the stock solution is added to a solution of N-methylbutylamine (118  $\mu$ L, 1 mmol) in anhydrous methylene  
15 chloride (1 mL), and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure.  
20 Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 1:1:1 tetrahydrofuran/methanol/water (3 mL), and lithium hydroxide monohydrate is added (33 mg, 0.75 mmol). The reaction is stirred 2 h and is concentrated under reduced  
25 pressure. The residue is redissolved in DMF (3 mL), and diisopropylethylamine (261  $\mu$ L, 1.5 mmol), HATU (214 mg, 0.56 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (189 mg, 0.37 mmol) are added. The reaction stirred at room temperature 16



h. Purification by flash column chromatography (silica, 8% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS  $m/z$  650.2  $[M + H]^+$ .

## EXAMPLE SP-183

3-[(Cyclohexylamino)methyl]-N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]-5-methylbenzamide dihydrochloride



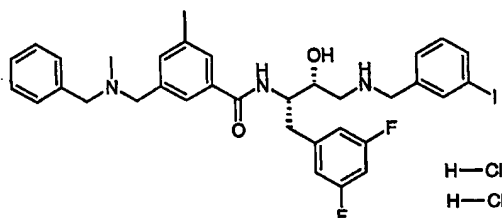
2 HCl

Analogous to the method described in EXAMPLE SP-177, Step 4, 2 mL of the stock solution is added to a solution of cyclohexylamine (114  $\mu$ L, 1 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 1:1:1 tetrahydrofuran/methanol/water (3 mL), and lithium hydroxide monohydrate is added (33 mg, 0.75 mmol). The reaction is stirred 2 h and is concentrated under reduced pressure. The residue is redissolved in DMF (3 mL), and diisopropylethylamine (261  $\mu$ L, 1.5 mmol), HATU (214 mg, 0.56 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (189 mg, 0.37

mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 8% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N  
5 hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS  $m/z$  662.2  $[M + H]^+$ .

## EXAMPLE SP-184

10 3-{[benzyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-5-methylbenzamide dihydrochloride



Analogous to the method described in EXAMPLE SP-177, a  
15 stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (1.0, 5.6 mmol) in methylene chloride (9 mL) at -30 °C is added methanesulfonyl chloride (600  $\mu$ L, 7.8 mmol) followed by triethylamine (1.55 mL, 11 mmol). The reaction mixture is stirred for 1 h at 0 °C, then filtered. From this stock  
20 solution, 2 mL is added to a solution of N-methylbenzylamine (538  $\mu$ L, 4.2 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 16 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with saturated sodium bicarbonate and brine, dried  
25 (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (90 mg, 2  
30 mmol). The reaction is stirred 16 h and is concentrated under

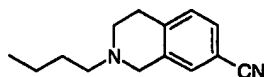
reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (695  $\mu$ L, 4 mmol), HATU (570 mg, 1.5 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (505 mg, 1 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 7% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS  $m/z$  684.2  $[M + H]^+$ .

## EXAMPLE SP-185

2-Butyl-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-1,2,3,4-tetrahydroisoquinoline-7-carboxamide dihydrochloride

## Step 1

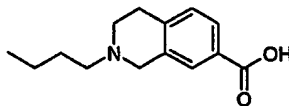
2-Butyl-1,2,3,4-tetrahydroisoquinoline-7-carbonitrile



To an ice-cold, stirred solution of 1,2,3,4-tetrahydroisoquinoline-7-carbonitrile (*J. Med. Chem.* **1997**, *40*, 3997) (485 mg, 3.1 mmol) and triethylamine (0.47 mL, 3.4 mmol) in methylene chloride (5 mL) is added DMAP (37 mg, 0.3 mmol) and bromobutane (0.5 mL, 4.6 mmol). The reaction mixture is stirred for 20 h, diluted with methylene chloride, washed with water, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl acetate/hexanes) affords the title compound. ESI MS  $m/z$  215  $[M + H]^+$ .

## Step 2

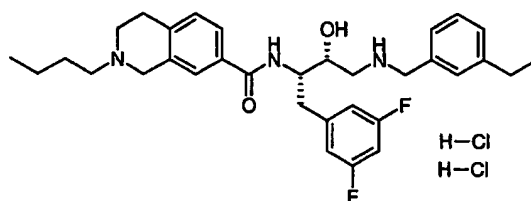
2-Butyl-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid



A sealed tube containing a solution of 2-butyl-1,2,3,4-tetrahydroisoquinoline-7-carbonitrile (480 mg, 2.2 mmol) in concentrated hydrochloric acid (10 mL) is stirred at 90 °C for 16 h. The reaction mixture is cooled to room temperature, concentrated ammonium hydroxide is added, and the precipitate formed is then collected by filtration to provide the title compound. ESI MS  $m/z$  234  $[M + H]^+$ .

### Step 3

2-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxamide dihydrochloride



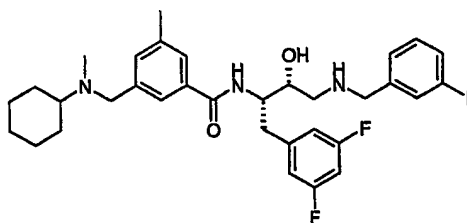
A solution of 2-butyl-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid (190 mg, 0.81 mmol), HATU (465 mg, 1.2 mmol), HOBT (162 mg, 1.2 mmol), and diisopropylethylamine (250  $\mu$ L, 1.6 mmol) is stirred in methylene chloride (2.0 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method in EXAMPLE SP-272 (332 mg, 0.81 mmol) and diisopropylethylamine (250  $\mu$ L, 1.6 mmol) in methylene chloride (2.0 mL) is added, and the reaction mixture is stirred overnight. The reaction mixture is diluted with methylene chloride, washed with 1 N hydrochloric acid (15 mL), saturated sodium bicarbonate (15 mL), and brine. The organic layer is then dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provides the title compound as the free

base. The solid is dissolved in methanol (1 mL), and treated with hydrochloric acid (0.2 mL, 1.0 M diethyl ether, 0.2 mmol). The resulting precipitate was collected by filtration to provide the title compound. ESI MS  $m/z$  550.3  $[M + H]^+$ .

5

## EXAMPLE SP-186

3-[[Cyclohexyl(methyl)amino]methyl]-N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl]-5-methylbenzamide dihydrochloride



2 HCl

10

Analogous to the method described in EXAMPLE SP-184, 2 mL of the stock solution is added to a solution of N-methylcyclohexylamine (545  $\mu$ L, 4.2 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 16 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with saturated sodium bicarbonate and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (60 mg, 1.4 mmol). The reaction is stirred 16 h and is concentrated under reduced pressure. The residue is redissolved in DMF (4 mL), and diisopropylethylamine (465  $\mu$ L, 2.7 mmol), HATU (380 mg, 1 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (340 mg, 0.67 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 7%

20

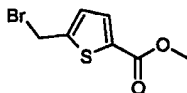
25

methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the  
5 title compound. ESI MS  $m/z$  676.2  $[M + H]^+$ .

## EXAMPLE SP-187

5- {[Butyl(methyl)amino]methyl}-N- {(1S,2R)-1-(3,5-  
difluorobenzyl)-3- [(3-ethylbenzyl)amino]-2-  
10 hydroxypropyl}thiophene-2-carboxamide dihydrochloride  
Step 1

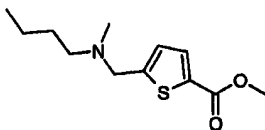
Methyl 5-(bromomethyl)thiophene-2-carboxylate



To an ice-cold solution of methyl 5-  
15 (hydroxymethyl)thiophene-2-carboxylate (375 mg, 2.17 mmol) in methylene chloride (9.0 mL) is added phosphorus tribromide (100  $\mu$ L, 1.08 mmol) and the reaction mixture is stirred at 0 °C for 0.5 h. Saturated sodium bicarbonate (10 mL) is  
20 carefully added to the reaction mixture and the phases are separated. The organic phase is washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield the title compound in pure form. ESI MS  $m/z$  235  $[M + H]^+$ .

## 25 Step 2

Methyl 5- {[butyl(methyl)amino]methyl}thiophene-2-carboxylate

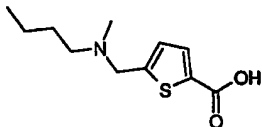


To a solution of methyl 5-(bromomethyl)thiophene-2-  
carboxylate (350 mg, 1.49 mmol) in dry acetone (6.0 mL) is  
30 added *N*-methylbutylamine (533  $\mu$ L, 4.47 mmol) and the solution stirred at room temperature overnight. The reaction is then

concentrated under reduced pressure, redissolved in methylene chloride, washed with saturated sodium bicarbonate, water, and brine. The organic layer is then dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield the  
5 title compound in pure form.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (d,  $J = 3$  Hz, 1H), 6.88 (d,  $J = 3$  Hz, 1H), 3.86 (s, 3H), 3.69 (s, 2H), 2.41–2.36 (m, 2H), 2.25 (s, 3H), 1.53–1.43 (m, 2H), 1.34–1.25 (m, 2H), 0.91 (t,  $J = 7$  Hz, 3H).

10 Step 3

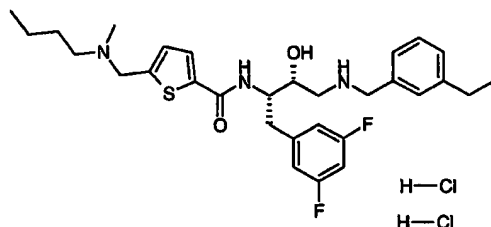
5-[[Butyl(methyl)amino]methyl]thiophene-2-carboxylic acid



To a solution of methyl 5-  
15 {[butyl(methyl)amino]methyl}thiophene-2-carboxylate (280 mg, 1.16 mmol) in 2:1:1 dioxane/methanol/water (8.0 mL) is added lithium hydroxide monohydrate (146 mg, 3.38 mmol) and the reaction mixture stirred at room temperature overnight. The reaction mixture is concentrated under reduced pressure and the solid residue partitioned between ethyl acetate and water  
20 The aqueous phase is acidified to pH 1 with 1 N hydrochloric acid and extracted several times with 3:1 chloroform/2-propanol. The combined organic phase is washed with water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide the title compound in pure  
25 form.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.75 (d,  $J = 4$  Hz, 1H), 7.41 (d,  $J = 4$  Hz, 1H), 4.63 (s, 2H), 3.20–3.14 (m, 2H), 2.85 (s, 3H), 1.82–1.72 (m, 2H), 1.42 (tq,  $J = 8, 7$  Hz, 2H), 0.99 (t,  $J = 7$  Hz, 3H).

30 Step 4

5-{{[Butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}thiophene-2-carboxamide dihydrochloride



5 To a solution 5-{{[butyl(methyl)amino]methyl}thiophene-2-carboxylic acid (171 mg, 0.75 mmol) and *N,N*-diisopropylethylamine (250 ~~μ~~L, 1.43 mmol) in methylene chloride (5.0 mL) is added HBTU (285 mg, 0.75 mmol) and the reaction stirred for 0.5 h. To this is added a solution of  
 10 (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method in EXAMPLE SP-272 (306 mg, 0.75 mmol) in methylene chloride (5.0 mL) containing *N,N*-diisopropylethylamine (250 ~~μ~~L, 1.43 mmol). The reaction mixture is then stirred at room temperature  
 15 overnight. The reaction mixture is diluted with methylene chloride, washed with saturated sodium bicarbonate, and brine. The organic layer is then dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 95:5 chloroform/methanol)  
 20 gives the title compound as the free base. The solid is dissolved in methanol (1 mL) and treated with hydrochloric acid (1.0 M diethyl ether). The resulting precipitate was collected by filtration to provide the title compound. ESI MS  $m/z$  544.3  $[M + H]^+$ .

25

#### EXAMPLE SP-188

3-{{[Butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-5-methylbenzamide dihydrochloride

30 Step 1